

THIAZOLYL UREA COMPOUNDS AND METHODS OF USES**Related Applications**

This application is a divisional of U.S. application
5 no. 10/077,124, filed February 15, 2002, which is a
continuation in part of U.S. application no. 09/930,753,
filed August 14, 2001, which claims the benefit of U.S.
provisional application no. 60/225,793, filed August 15,
2000, all of which are incorporated by reference herein.

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FIELD OF THE INVENTION

This invention is in the field of pharmaceutical
agents and specifically relates to compounds, compositions,
uses and methods for treating cell proliferation-related
15 disorders, cell death and apoptosis-related disorders.

BACKGROUND OF THE INVENTION

Identification of therapeutic agents effective in the
treatment of neoplastic diseases or for the treatment of
20 neurological disorders is the subject of significant
research efforts.

Protein kinases represent a large family of proteins
which play a central role in the regulation of a wide
variety of cellular processes and maintaining control over
25 cellular function. A partial list of such kinases includes
abl, Akt, bcr-abl, Blk, Brk, Btk, c-kit, c-met, c-src,
CDK1, CDK2, CDK3, CDK4, CDK5, CDK6, CDK7, CDK8, CDK9,
CDK10, cRaf1, CSF1R, CSK, EGFR, ErbB2, ErbB3, ErbB4, Erk,
Fak, fes, FGFR1, FGFR2, FGFR3, FGFR4, FGFR5, Fgr, FLK-4,
30 flt-1, Fps, Frk, Fyn, Hck, IGF-1R, INS-R, Jak, KDR, Lck,
Lyn, MEK, p38, PDGFR, PIK, PKC, PYK2, ros, tie, tie2, TRK,
Yes, and Zap70. As such, inhibition of kinases has become
an important therapeutic target.

Cell proliferation is the rapid reproduction of cells,
35 such as by cell division. The cell cycle, which controls

cell proliferation, is itself controlled by a family of serine-threonine kinases called cyclin dependent kinases (CDKs). The regulation of CDK activation is complex, and requires the association of the CDK with a member of the 5 cyclin family of regulatory subunits. A further level of regulation occurs through both activating and inactivating phosphorylations of the CDK subunit. The coordinate activation and inactivation of different cyclin/CDK complexes is necessary for normal progression through the 10 cell cycle. Both the critical G1-S and G2-M transitions are controlled by the activation of different cyclin/CDK activities. Loss of control of CDK regulation is a frequent event in hyperproliferative diseases and cancer.

(T. Noguchi et al., Am. J. Pathol., 156, 2135-47 (2000))
15 As such, inhibition of CDKs has become an important target in the study of therapeutics (A. Senderowicz and E. Sausville, J. Nat. Canc. Inst., 92, 376-87 (2000))

Kinases have also been implicated in diseases and disorders of the central nervous system. For example, 20 patients suffering from stroke, Alzheimer's disease or Parkinson's disease would benefit from the inhibition of kinases. Cdk5 has been shown to be involved in Alzheimer's pathology (R. Maccioni, et al., Eur. J. Biochem., 268, 1518-27 (2001)) and with neuronal development (G. Paglini 25 and A. Caceres, Eur. J. Biochem., 268, 1528-33 (2001)).

Protein kinases also control programmed cell death, also known as apoptosis. Apoptosis is a ubiquitous physiological process used to eliminate damaged or unwanted cells in multicellular organisms. Disregulation of 30 apoptosis is believed to be involved in the pathogenesis of many human diseases. The failure of apoptotic cell death has been implicated in various cancers, as well as autoimmune disorders. Conversely, increased apoptosis is associated with a variety of diseases involving cell loss

such as neurodegenerative disorders and AIDS. As such, inhibition of apoptosis has become an important therapeutic target. Cdk5 has been shown to be involved in apoptosis pathology (A. Catania et al., Neuro-Oncology, 89-98 (April 5 2001)).

Substituted heterocyclic compounds are known in the pesticide art. WO00/24735, published 4 May 2000, describes 1-pyridyl-1,2,4-triazoles as pesticides. WO00/24739, published 4 May 2000, describes substituted 1,2,4-triazoles 10 as pesticides. WO97/01552, published 16 January 1997, describes substituted 1,2,4-triazoles as antifungal agents. DE4204492 describes substituted benzamides as pesticides. WO98/57969, published 23 December 1998, describes 15 heterocyclypyridines as pesticides. GB2293380, published 27 March 1996, describes the use of heterocyclic compounds as pesticides. United States patent No. 5,693,667, issued Dec. 2, 1997, describes heterocyclic compounds for the treatment of take-all disease. EP468695 describes fungicide 20 compounds. United States patent No. 5,294,596, issued March 15, 1994, describes herbicidal triazolinones. United States patent No. 5,395,818, issued March 7, 1995, describes herbicidal triazolinones.

Substituted thiazoles also are known in the pesticide art. United States patent No. 4,260,765, issued Apr. 7, 25 1981, describes 2-(3-pyridyl)-5-thiazolecarboxamides for the treatment of aphids. United States patent No. 5,945,380, issued Aug. 31, 1999, describes 4-(4-pyridyl)pyrazoles as insecticides. WO89/00568, published 26 January 1989, describes nicotine derivatives as fungicides.

30 Heterocyclic ureas are known in the pharmaceutical art. WO99/23091, published 14 May 1999, describes heterocyclic compounds as anti-inflammatories. WO99/32455, published 1 July 1999, describes heterocyclic ureas as RAF kinase inhibitors. WO99/32110, published 1 July 1999,

describes heterocyclic ureas as p38 kinase inhibitors. WO99/32106, published 1 July 1999, describes heterocyclic ureas as RAF kinase inhibitors. WO99/32111, published 1 July 1999, describes heterocyclic ureas as p38 kinase inhibitors. WO99/32436, published 1 July 1999, describes urea compounds as inhibitors of RAF kinase. WO99/32463, published 1 July 1999, describes urea compounds that inhibit p38 kinase. WO98/52558, published 26 November 1998, describes urea compounds for the inhibition of p38 kinase.

10 WO99/00357, published 7 January 1999, describes the use of urea compounds as inhibitors of p38 kinase. WO99/58502, published 18 November 1999, describes urea compounds as inhibitors of p38 kinase. US patent 5,821,245, issued Oct. 13, 1998, describes substituted naphthalene derivatives for

15 treating cell growth. GB patent 1,437,895 describes 2-thiazolyl ureas for the treatment of ulcers. United States patent 5,364,871, issued Nov. 15, 1994 describes thiazoles as anti-ulcer compounds. WO99/21555, published 6 May 1999, describes pyridyl-substituted thiazoles as adenosine A3

20 receptor antagonists. WO96/23783 describes indole derivatives as 5-HT receptor antagonists. United States patent No. 5,208,248 describes indazole derivatives as 5-HT receptor antagonists. WO99/46244, published 16 September 1999 describes heterocyclic compounds as tyrosine

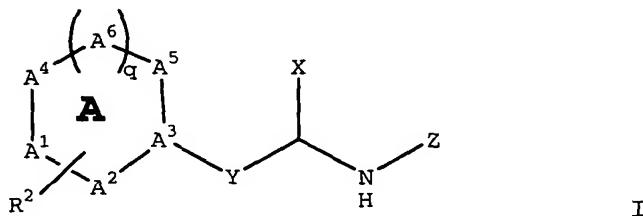
25 phosphatases. GB patent 2,263,109, published 14 July 1993, describes pyridylthiazoles as PAF-receptor antagonists.

Thiazole compounds have also been described as inhibitors of CDK. WO00/26203, published 11 May 2000, describes 2-ureidothiazoles as inhibitors of cdk.

30 WO99/65884 describes 2-aminothiazoles as inhibitors of CDK. WO99/24416 describes 2-aminothiazoles as inhibitors of CDK. However, compounds of the current invention have not been described as inhibitors of cell proliferation or apoptosis such as for the treatment of cancer or stroke.

DESCRIPTION OF THE INVENTION

A class of compounds useful in treating cell
 5 proliferative disorders, neurological disorders and
 apoptosis is defined by Formula I



10

wherein each of A¹-A⁶ is selected from CH₂, CH, C, O, S, NH and N; wherein A¹-A⁶ together form a ring A selected from

a) additionally substituted or unsubstituted 5- or 6-membered heterocyclyl,

15

preferably 5- or 6-membered heteroaryl,

more preferably 5-membered heteroaryl selected from thiazolyl, oxazolyl, imidazolyl, pyrrolyl, pyrazolyl, isoxazolyl, triazolyl and isothiazolyl, and

20

6-membered heteroaryl selected from pyridyl, pyrazinyl, pyrimidinyl and pyridazinyl,

even more preferably 5-membered heteroaryl selected from thiazolyl, oxazolyl and imidazolyl, and 6-membered heteroaryl selected from pyridyl, and pyrimidinyl,

25

b) additionally substituted or unsubstituted 5- or 6-membered heteroaryl fused with a phenyl group,

c) additionally substituted or unsubstituted 5- or 6-membered cycloalkenyl,

30

preferably 5-membered cycloalkenyl,

more preferably cyclopentadienyl or cyclopentenyl,
and

d) additionally substituted or unsubstituted phenyl,

wherein A is additionally substituted with one or more

5 substituents independently selected from halo, -OR³, -SR³,
-CO₂R³, -CO₂NR³R³, -COR³, -NR³R³, -SO₂NR³R³, -NR³C(O)OR³, -
NR³C(O)R³, cycloalkyl, optionally substituted
phenylalkylenyl, optionally substituted 5-6 membered
heterocyclyl, optionally substituted heteroarylalkylenyl,
10 optionally substituted phenyl, lower alkyl, cyano, lower
hydroxyalkyl, nitro, lower alkenyl, lower alkynyl and
lower haloalkyl,

15 preferably one or more substituents independently
selected from halo, -OR³, -SR³, -S(O)R³, -CO₂R³, -
CO₂NR³R³, -COR³, -NR³R³, -SO₂NR³R³, -NR³C(O)OR³, -
NR³C(O)R³, C₁-C₂ alkyl, cyano, C₁-C₂ hydroxyalkyl,
nitro, C₂-C₃ alkenyl, C₂-C₃ alkynyl and C₁-C₂ haloalkyl,
more preferably one or more substituents independently
selected from fluoro, hydroxy, methoxy, amino and
20 methyl;

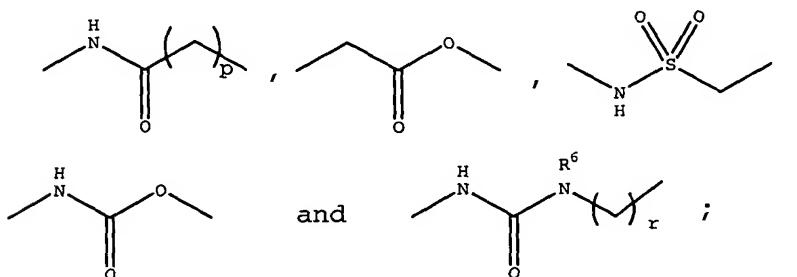
wherein X and Z taken together form a nitrogen containing
ring selected from
unsubstituted 5-6 membered heterocyclyl,
unsubstituted 5-6 membered heterocyclyl fused with a
25 phenyl group,
5-6 membered heterocyclyl substituted with one or more
substituents independently selected from R¹, and
5-6 membered nitrogen-containing heterocyclyl,
fused with a phenyl group, substituted with one
30 or more substituents independently selected from
R¹,
preferably a ring selected from substituted or
unsubstituted 5- or 6-membered nitrogen-containing
heteroaryl, and substituted or unsubstituted 5- or 6-

membered nitrogen-containing heteroaryl fused with a phenyl group,
more preferably substituted or unsubstituted thiazolyl,
5 triazinyl, isoindolyl, indolyl, indazolyl, purinyl,
[1,6]naphthyridinyl, 5,6,7,8-
tetrahydro[1,6]naphthyridinyl, isoquinolyl and
quinolyl,
even more preferably pyridyl, pyrazinyl, pyrimidinyl,
10 pyridazinyl, [1,6]naphthyridinyl and 5,6,7,8-
tetrahydro[1,6]naphthyridinyl,
most preferably pyridyl, pyrazinyl, pyrimidinyl and
pyridazinyl,
most preferred pyridyl;
15 wherein R¹ is independently selected from H, halo, -OR³, -
SR³, -CO₂R³, -CO₂NR³R³, -COR³, -CONR³R³, -NR³R³, -
C(S)NR³R³, -SO₂NR³R³, -NR³C(O)OR³, -NR³C(O)R³, cycloalkyl,
optionally substituted phenylalkenyl, optionally
substituted 4-10 membered heterocyclyl, optionally
20 substituted 4-10 membered heterocyclylalkyl, optionally
substituted phenyl, optionally substituted phenoxy,
lower alkyl, lower cyano, lower alkenyl, lower alkynyl
and lower haloalkyl,
preferably optionally substituted pyrrolidinyl,
25 optionally substituted piperazinyl, optionally
substituted piperidinyl, morpholinyl, optionally
substituted pyridyl, 1,4-dioxa-8-aza-spiro[4.5]decyl,
optionally substituted phenyl, C₁-C₄ alkyl, C₁-C₂
haloalkyl, halo, C₁-C₄-hydroxyalkyl, amino, C₁-C₄-
30 azidoalkyl, C₁-C₄-cyanoalkyl, C₁-C₄-aminoalkyl, hydroxy,
C₁-C₄-alkoxy-C₁-C₄-alkyl, C₁-C₄-alkylamino-C₁-C₄-alkyl,
C₁-C₄-hydroxyalkylamino-C₁-C₄-alkyl, amino-C₁-C₄-alkoxy-
C₁-C₄-alkyl, C₁-C₄-alkylamino-C₁-C₄-alkylamino-C₁-C₄-
alkyl, (optionally substituted pyrrolidinyl)-C₁-C₂-

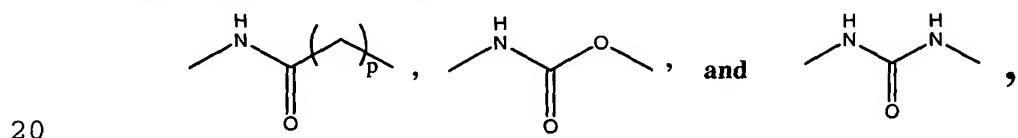
alkyl, (optionally substituted piperidinyl)-C₁-C₂-
alkyl, (optionally substituted piperazinyl)-C₁-C₂-
alkyl, 4-morpholinyl-C₁-C₂-alkyl, (optionally
substituted imidazolyl)-C₁-C₂-alkyl, phthalimidylethyl,
5
optionally substituted azepanyl-C₁-C₂-alkyl, 1,4-dioxa-
8-aza-spiro[4.5]decyl-C₁-C₂-alkyl, optionally
substituted pyridyloxy, optionally substituted
phenoxy, tetrahydrofuryl-O-, (1-aza-bicyclo[2.2.2]oct-
3-yl)-oxy, optionally substituted phenoxy-C₁-C₂-alkyl,
10
optionally substituted pyrrolidinyl-C₁-C₄-alkoxy,
optionally substituted azetidinyl-C₁-C₄-alkoxy,
optionally substituted piperidinyl-C₁-C₄-alkoxy,
tetrahydrofuryl-C₁-C₄-alkoxy, C₁-C₄-alkylamino-C₁-C₄-
alkoxy morpholinyl-C₁-C₄-alkylenylaminocarbonyl, C₁-C₄-
15
alkoxycarbonyl, 5-6-membered heterocyclyl-C₁-C₄-
alkylaminocarbonyl, 5-6-membered N-containing
heterocyclylcarbonyl, C₁-C₄-alkylaminocarbonyl, C₁-C₄-
alkylamino-C₁-C₄-alkylaminocarbonyl, 5-6-membered N-
containing heterocyclyl-C₁-C₄-alkylamino,
20
aminocarbonyl, C₁-C₃-alkylaminothiocarbonyl, C₁-C₄-
alkylamino and C₁-C₄-alkylamino-C₁-C₄-alkylamino,
more preferably 3-(N,N-dimethylamino)-1-pyrrolidinyl, 1-
methyl-4-piperazinyl, 1-benzyl-4-piperazinyl, 1-(2-
pyrimidinyl)-4-piperazinyl, 1-(2-pyridyl)-4-
25
piperazinyl, 1-ethyl-4-piperazinyl, piperidinyl,
morpholinyl, 4-amino-1-piperidinyl, 4-(N-
hydroxyethylamino)-1-piperidinyl, 4-(N-propylamino)-1-
piperidinyl, 4-(N-benzylamino)-1-piperidinyl, 4-oxo-
piperidinyl, 4-(hydroxyimino)-piperidinyl, 4-
30
morpholinyl, 1,4-dioxa-8-aza-spiro[4.5]decyl, pyridyl,
phenyl, methyl, ethyl, propyl, isopropyl, butyl, sec-
butyl, isobutyl, tert-butyl, amino, azidomethyl,
hydroxymethyl, trifluoromethyl, difluoromethyl,
pentafluoroethyl, fluoro, chloro, bromo, aminoethyl,

aminomethyl, cyanomethyl, 1-pyrrolidinyl-CH₂-, 2-methoxycarbonyl-1-pyrrolidinyl-CH₂-, 2-carboxy-1-pyrrolidinyl-CH₂-, 2-hydroxymethyl-1-pyrrolidinyl-CH₂-, 1-piperidinyl-CH₂-, 4-methyl-1-piperidinyl-CH₂-, 3-methyl-1-piperidinyl-CH₂-, 2-methyl-1-piperidinyl-CH₂-, 5
3,5-dimethyl-1-piperidinyl-CH₂-, 4-oxo-1-piperidinyl-CH₂-, 4-hydroxy-1-piperidinyl-CH₂-, 3-hydroxy-1-piperidinyl-CH₂-, 2-ethoxycarbonyl-1-piperidinyl-CH₂-, 3-ethoxycarbonyl-1-piperidinyl-CH₂-, 3-carboxy-1-piperidinyl-CH₂-, 10 4-ethoxycarbonyl-1-piperidinyl-CH₂-, 4-carboxy-1-piperidinyl-CH₂-, 4-(1-pyrrolidinyl)-1-piperidinyl-CH₂-, 4-(N-hydroxyethylamino)-1-piperidinyl-CH₂-, 4-(N-propylamino)-1-piperidinyl-CH₂-, 15 1-methyl-4-piperazinyl-CH₂-, 4-morpholinyl-CH₂-, (2-methyl-1-imidazolyl-CH₂-, 3-(N,N-diethylamino)carbonyl-1-piperidinyl-CH₂-, phthalimidylethylene, 1-azepanyl-CH₂-, 1,4-dioxa-8-aza-spiro[4.5]decyl-CH₂-, 4-(methyl)phenoxyethylene, 4-(N,N-dimethylaminomethylenyl)phenoxyethylene, 20 4-(N,N-dimethylaminothiocarbonyl)phenoxyethylene, 4-(N,N-dimethylaminomethylenyl), N,N-dimethylaminoethylene, N,N-dimethylaminomethylenyl, N-methylaminoethylene, N-methylaminomethylenyl, N-(hydroxypropyl)aminomethylenyl, N-ethylaminomethylenyl, Boc-aminoethoxymethylenyl, 25 aminoethoxymethylenyl, (1-aza-bicyclo[2.2.2]oct-3-yl)-oxy, 2-pyrrolidinylmethoxy, 1-methyl-2-pyrrolidinylmethoxy, azetidin-3-ylmethoxy, N-Boc-azetidin-3-ylmethoxy, N-Boc-piperidin-4-ylethoxy, 1-methyl-4-piperidinylethoxy, 4-piperidinylethoxy, 4-piperidinylmethoxy, N,N-dimethylaminoethoxy, 30 3-tetrahydrofuryl-O-, 3-tetrahydrofurylmethoxy, 4-tetrahydrofurylmethoxy, 4-methylphenoxy, 4-(aminoethyl)phenoxy, 4-(1-imidazolyl)phenoxy, 2,4-

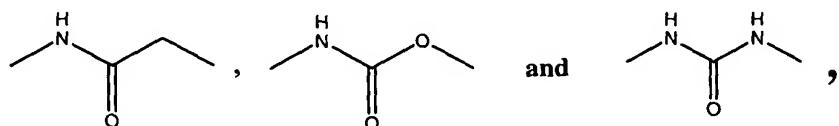
dimethylphenoxy, phenoxy, 4-cyanophenoxy, 4-[1,3]dioxolan-2-ylphenoxy, 4-fluorophenoxy, 3,4-difluorophenoxy, ethoxycarbonyl,
 5 morpholinylethyleneaminocarbonyl,
 morpholinylpropylenylaminocarbonyl, 1-piperidinylcarbonyl, methylaminocarbonyl,
 ethylaminocarbonyl, N,N-diethylaminocarbonyl, N-(N',N'-dimethylaminoethylenyl)aminocarbonyl,
 aminocarbonyl, morpholinylethyleneamino,
 10 morpholinylpropylenylamino, N,N-diethylamino, N,N-dimethylamino, N,N-diethylamino(2-propylenyl)aminomethylenyl, N,N-diethylamino(1-propylenyl)aminomethylenyl and N-(N',N'-dimethylaminoethylenyl)amino;
 15 wherein Y is selected from

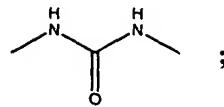


preferably Y is selected from



more preferably Y is selected from





wherein R² is selected from

- a) lower alkylaminoalkynyl,
- 5 b) cycloalkenyl-C₂₋₃-alkynyl,
- c) cycloalkyl-C₂₋₃-alkynyl,
- d) phenyl-C₂₋₃-alkynyl,
- e) 5-6 membered heterocyclyl-C₂₋₃-alkynyl,
- f) substituted or unsubstituted cycloalkenyl,
- 10 g) substituted or unsubstituted phenyl,
- h) substituted or unsubstituted 5-6 membered heterocyclyl, and
- i) substituted or unsubstituted 5-6 membered heterocyclyl bridged with a phenyl group,
- 15 preferably substituted phenyl, substituted or unsubstituted 5-6 membered nitrogen-containing heteroaryl, and substituted or unsubstituted 5-6 membered nitrogen-containing heteroaryl fused with a phenyl group,
- 20 more preferably substituted or unsubstituted substituted phenyl or a substituted or unsubstituted heterocyclyl substituent selected from thiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, isoindolyl, indolyl, indazolyl, purinyl, isoquinolyl and quinolyl,
- 25 even more preferably phenyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, purinyl, isoquinolyl and quinolyl,
- most preferably pyridyl, pyrazinyl, pyrimidinyl and pyridazinyl,
- 30 preferred pyridyl;

wherein substituted R² is substituted with one or more substituents independently selected from halo, -OR³, -SR³, -CO₂R³, -CO₂NR³R³, -COR³, -NR³R³, -C(O)NR³R³, -SO₂NR³R³, -NR³C(O)OR³, -NHC(O)R³, -SO₂NHC(O)R³, -C(S)NR³R³, nitro,

5 cycloalkyl, optionally substituted phenylalkylenyl, optionally substituted 4-7 membered heterocyclyl, optionally substituted heterocyclylalkylenyl, optionally substituted phenyl, optionally substituted phenoxyalkylenyl, optionally substituted

10 heterocyclyloxyalkyl, lower alkyl, cyano, lower hydroxyalkyl, lower alkoxyalkyl, lower azidoalkyl, lower aminoalkyl, lower (hydroxyalkyl)aminoalkyl, lower alkylaminoalkyl, lower alkylaminoalkoxy, lower aminoalkoxyalkyl, lower (alkylaminoalkyl)amino lower

15 ((alkylamino)alkylamino)alkyl, lower alkylaminoalkylaminocarbonyl, lower cyanoalkyl, lower alkenyl, lower alkynyl and lower haloalkyl, preferably selected from C₁-C₄ alkyl, C₁-C₂ haloalkyl, halo, amino, C₁-C₂-alkoxy, C₁-C₂-alkoxy-C₁-C₂-alkyl,

20 hydroxy, C₁-C₂-alkylthio, cyano, C₁-C₂-haloalkyloxy, aminosulfonyl, (6-membered N-containing heterocyclyl)sulfonyl, C₁-C₂-haloalkylaminocarbonyl, nitro, C₁-C₂-haloalkylcarbonylaminosulfonyl, C₁-C₂-alkylaminosulfonyl, C₃-C₆-cycloalkylaminosulfonyl,

25 phenyl-C₁-C₂-alkylaminosulfonyl, (optionally substituted phenyl)aminosulfonyl, piperidinyl, morpholinyl, C₁-C₂ alkylpiperazinyl, C₁-C₃ alkylaminothiocarbonyl, C₁-C₂-alkylamino-C₁-C₄-alkylenyl, morpholinyl-C₁-C₄-alkylenylaminocarbonyl, aminocarbonyl, C₁-C₂-alkylcarbonylamino, morpholinyl-C₁-C₄-alkylenylamino, C₁-C₂-alkylamino and C₁-C₂-alkylamino-C₁-C₄-alkylenylamino,

30 more preferably selected from nitro,

wherein p is 1-2, preferably p is 1;

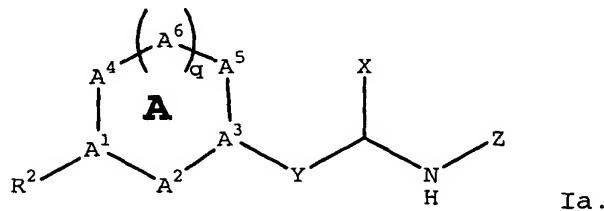
wherein q is 0 or 1; and

wherein r is 0, 1, 2 or 3, preferably 0 or 1, more
preferably 0;

5 and pharmaceutically acceptable salts thereof;
provided A is not thiazol-2-yl when Y is ureido; further
provided A is not phenyl when R² is pyridyl or pyrimidyl
when Y is ureido and when X and Z taken together form 1-
methylindolyl; further provided A is not 1-phenylpyrazol-
10 4-yl when Y is ureido when X and Z taken together form
pyrazolyl and when R² is pyrrol-1-yl; further provided A
is not thiazolyl or dihydrothiazolyl when R² is indolyl
when Y is ureido and when X and Z taken together form
thiazolyl or dihydrothiazolyl; provided A is not
15 thiazolyl when R² is 3-pyridyl when Y is ureido and when
X and Z taken together form 2-(3-pyridyl)thiazol-4-yl;
and further provided A is not thien-3-yl when Y is ureido
when X and Z taken together form thienyl and when R² is
pyrrol-1-yl.

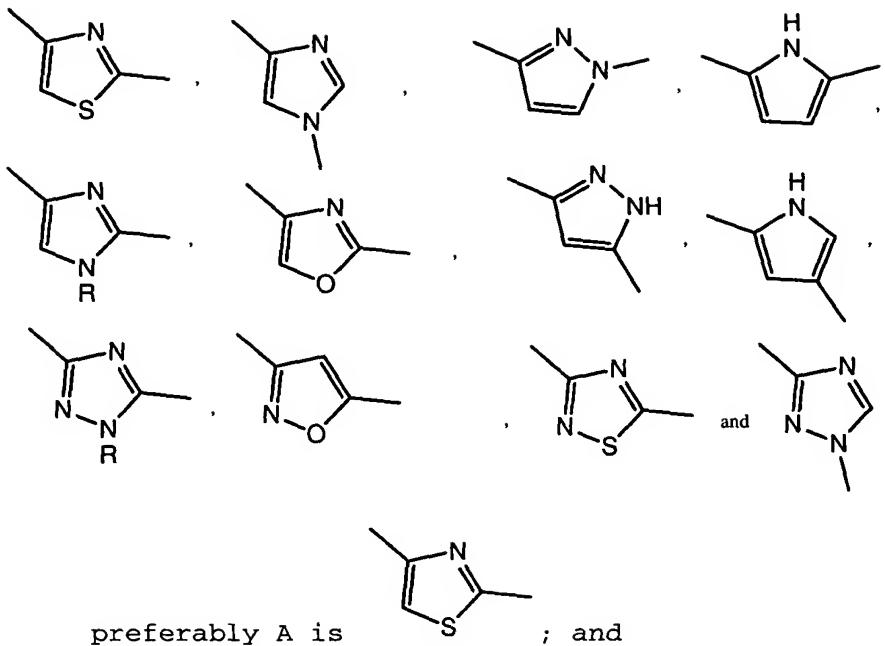
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The invention also relates to compounds of Formula Ia



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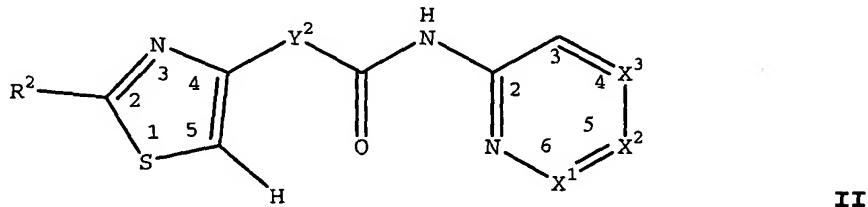
The invention also relates to compounds of Formula I
wherein A is selected from



wherein R is selected from H and C₁-C₃ alkyl; and pharmaceutically acceptable salts thereof.

5

The invention also relates to compounds of Formula II



10 wherein X¹ is CR¹ or N; wherein X² is CR¹ or N; wherein X³ is CH or N; provided only one of X¹, X² and X³ can be N; wherein R¹ is one or more substituents selected from H, optionally substituted pyrrolidinyl, optionally substituted piperazinyl, optionally substituted piperidinyl, morpholinyl, 1,4-dioxa-8-aza-spiro[4.5]decyl, pyridyl, phenyl, C₁-C₆-alkyl, C₁-C₂-haloalkyl, C₁-C₄-hydroxyalkyl, amino, C₁-C₄-azidoalkyl, C₁-C₄-cyanoalkyl, C₁-C₄-aminoalkyl, halo, hydroxy,

15

(optionally substituted pyrrolidinyl)-C₁-C₂-alkyl,
(optionally substituted piperidinyl)-C₁-C₂-alkyl,
(optionally substituted piperazinyl)-C₁-C₂-alkyl,
morpholinyl-C₁-C₂-alkyl, (optionally substituted
5 imidazolyl)-C₁-C₂-alkyl, phthalimidyl-C₁-C₂-alkyl,
optionally substituted azepanyl-C₁-C₂-alkyl, 1,4-dioxa-8-
az-a-spiro[4.5]decyl-C₁-C₂-alkyl, optionally substituted
phenoxy-C₁-C₂-alkyl, C₁-C₄-alkylaminothiocarbonyl, C₁-C₄-
alkoxy-C₁-C₄-alkyl, C₁-C₄-alkylamino-C₁-C₄-alkyl, C₁-C₄-
10 hydroxyalkylamino-C₁-C₄-alkyl, amino-C₁-C₄-alkoxy-C₁-C₄-
alkyl, (1-aza-bicyclo[2.2.2]oct-3-yl)-oxy, optionally
substituted pyrrolidinyl-C₁-C₄-alkoxy, optionally
substituted azetidinyl-C₁-C₄-alkoxy, optionally
substituted piperidinyl-C₁-C₄-alkoxy, C₁-C₄-alkylamino-C₁-
15 C₄-alkoxy, tetrahydrofuryl-0-, tetrahydrofuryl-C₁-C₄-
alkoxy, optionally substituted pyridyloxy, optionally
substituted phenoxy, C₁-C₄-alkoxycarbonyl, 5-6-membered
heterocyclyl-C₁-C₄-alkylaminocarbonyl, 5-6-membered N-
containing heterocyclylcarbonyl, C₁-C₄-alkylaminocarbonyl,
20 C₁-C₄-alkylamino-C₁-C₄-alkylaminocarbonyl, aminocarbonyl,
5-6-membered N-containing heterocyclyl-C₁-C₄-alkylamino,
C₁-C₄-alkylamino, C₁-C₄-alkylamino-C₁-C₄-alkylamino-C₁-C₄-
alkyl, and C₁-C₄-alkylamino-C₁-C₄-alkylamino;
wherein R² is selected from halo, C₁-C₄-alkyl, C₁-C₄-
25 alkylamino-C₂-C₄-alkynyl, C₃-C₆-cycloalkyl, optionally
substituted benzodioxolyl, optionally substituted
indolyl, optionally substituted phenoxy, unsubstituted
5-membered oxygen or sulfur containing heteroaryl,
unsubstituted 6-membered nitrogen-containing
heterocyclyl, phenyl optionally substituted with one or
30 two substituents selected
from halo, C₁-C₄-alkylamino, amino, nitro, C₁-C₄-
alkoxy, C₁-C₂-haloalkyl, hydroxy, C₁-C₄-alkylthio, C₁-
C₄-alkylcarbonylamino, (optionally substituted

phenyl)sulfonylamino, cyano, C₁-C₂-haloalkoxy, 5- or 6-membered N-containing heterocyclyl, aminosulfonyl, (6-membered N-containing heterocyclyl)sulfonyl, C₁-C₂-haloalkylcarbonylaminosulfonyl and (optionally substituted phenyl)aminosulfonyl, and

5 6-membered nitrogen-containing heterocyclyl substituted with one or more substituents independently selected from pyridyl, phenyl,

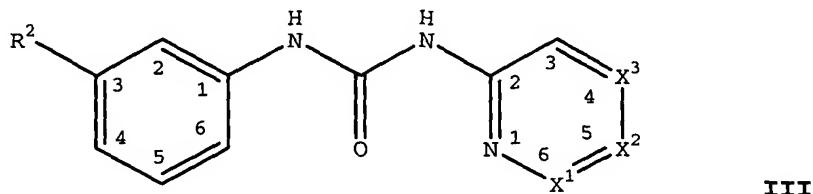
10 C₁-C₄ alkyl, C₁-C₂ haloalkyl, C₁-C₂ alkoxy, amino, halo, piperidinyl, morpholinyl, C₁-C₂ alkylpiperazinyl, C₁-C₃ alkylaminothiocarbonyl, N,N-di-C₁-C₂-alkylamino-C₁-C₄-alkylenyl, N-C₁-C₂-alkylamino-C₁-C₄-alkylenyl, morpholinyl-C₁-C₄-alkylenylaminocarbonyl, aminocarbonyl, C₁-C₂-haloalkylcarbonylamino, morpholinyl-C₁-C₄-alkylenylamino, N,N-di-C₁-C₂-alkylamino and N,N-di-C₁-C₂-alkylamino-C₁-C₄-alkylenylamino; and

15 wherein Y² is selected from O, NH and CH₂;

wherein Y² is selected from O, NH and CH₂;

20 and pharmaceutically acceptable salts thereof.

The invention also relates to compounds of Formula III



25 wherein X¹ is CR¹ or N; wherein X² is CR¹ or N; wherein X³ is CH or N; provided only one of X¹, X² and X³ can be N; preferably X¹ is CR¹; X² is CR¹; X³ is CH; provided X² is CH when X¹ is not CH;

wherein R¹ is one or more substituents independently

30 selected from H, optionally substituted pyrrolidinyl, optionally substituted piperazinyl, optionally

substituted piperidinyl, morpholinyl, 1,4-dioxa-8-aza-spiro[4.5]decyl, pyridyl, phenyl, C₁-C₆-alkyl, C₁-C₂-haloalkyl, C₁-C₄-hydroxyalkyl, amino, C₁-C₄-azidoalkyl, C₁-C₄-cyanoalkyl, C₁-C₄-aminoalkyl, halo, hydroxy.

5 (optionally substituted pyrrolidinyl)-C₁-C₂-alkyl, (optionally substituted piperidinyl)-C₁-C₂-alkyl, (optionally substituted piperazinyl)-C₁-C₂-alkyl, morpholinyl-C₁-C₂-alkyl, (optionally substituted imidazolyl)-C₁-C₂-alkyl, phthalimidyl-C₁-C₂-alkyl,

10 optionally substituted azepanyl-C₁-C₂-alkyl, 1,4-dioxa-8-aza-spiro[4.5]decyl-C₁-C₂-alkyl, optionally substituted phenoxy-C₁-C₂-alkyl, C₁-C₄-alkylaminothiocarbonyl, C₁-C₄-alkoxy-C₁-C₄-alkyl, C₁-C₄-alkylamino-C₁-C₄-alkyl, C₁-C₄-hydroxyalkylamino-C₁-C₄-alkyl, amino-C₁-C₄-alkoxy-C₁-C₄-alkyl, (1-aza-bicyclo[2.2.2]oct-3-yl)-oxy, optionally substituted pyrrolidinyl-C₁-C₄-alkoxy, optionally substituted azetidinyl-C₁-C₄-alkoxy, optionally substituted piperidinyl-C₁-C₄-alkoxy, C₁-C₄-alkylamino-C₁-C₄-alkoxy, tetrahydrofuryl-O-, tetrahydrofuryl-C₁-C₄-alkoxy, optionally substituted pyridyloxy, optionally substituted phenoxy, C₁-C₄-alkoxycarbonyl, 5-6-membered heterocyclyl-C₁-C₄-alkylaminocarbonyl, 5-6-membered N-containing heterocyclylcarbonyl, C₁-C₄-alkylaminocarbonyl, C₁-C₄-alkylamino-C₁-C₄-alkylaminocarbonyl, aminocarbonyl,

15 20 25 30 5-6-membered N-containing heterocyclyl-C₁-C₄-alkylamino, C₁-C₄-alkylamino, C₁-C₄-alkylamino-C₁-C₄-alkylamino-C₁-C₄-alkyl, and C₁-C₄-alkylamino-C₁-C₄-alkylamino, preferably H, methyl, ethyl, propyl, 1-methyl-4-piperazinyl, 1-benzyl-4-piperazinyl, 1-(2-pyrimidinyl)-4-piperazinyl, 1-(2-pyridyl)-4-piperazinyl, 1-ethyl-4-piperazinyl, 1-piperidinyl-CH₂-, 4-methyl-1-piperidinyl-CH₂-, 3-methyl-1-piperidinyl-CH₂-, 2-methyl-1-piperidinyl-CH₂-, 3,5-dimethyl-1-piperidinyl-CH₂-, 4-oxo-1-piperidinyl-CH₂-, 4-hydroxy-

1-piperidinyl-CH₂-, 3-hydroxy-1-piperidinyl-CH₂-, 2-ethoxycarbonyl-1-piperidinyl-CH₂-, 3-ethoxycarbonyl-1-piperidinyl-CH₂-, 3-carboxy-1-piperidinyl-CH₂-, 4-ethoxycarbonyl-1-piperidinyl-CH₂-, 4-carboxy-1-piperidinyl-CH₂-, 4-(1-pyrrolidinyl)-1-piperidinyl-CH₂-, 4-(N-hydroxyethylamino)-1-piperidinyl-CH₂-, 4-(N-propylamino)-1-piperidinyl-CH₂-, 3-(N,N-diethylamino)carbonyl-1-piperidinyl-CH₂-, 4-morpholinyl-CH₂-, N,N-dimethylaminoethylenyl, N,N-diethylaminomethylenyl, N-methylaminomethylenyl, N-ethylaminomethylenyl and N,N-diethylamino, more preferably ethyl, propyl, 1-methyl-4-piperazinyl, 1-piperidinyl-CH₂-, 4-morpholinyl-CH₂-, N,N-diethylaminomethylenyl and N,N-diethylamino; and

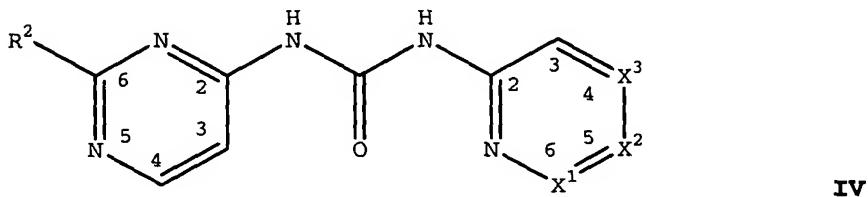
15 wherein R² is selected from halo, C₁-C₄-alkyl, C₁-C₄-alkylamino-C₂-C₄-alkynyl, C₃-C₆-cycloalkyl, optionally substituted benzodioxolyl, optionally substituted indolyl, optionally substituted phenoxy, unsubstituted 5-membered oxygen or sulfur containing heteroaryl, 20 unsubstituted 5- or 6-membered nitrogen-containing heterocyclyl, phenyl optionally substituted with one or two substituents selected from halo, C₁-C₄-alkylamino, amino, nitro, C₁-C₄-alkoxy, C₁-C₂-haloalkyl, hydroxy, C₁-C₄-alkylthio, C₁-C₄-alkylcarbonylamino, (optionally substituted phenyl)sulfonylamino, cyano, C₁-C₂-haloalkoxy, 5- or 25 6-membered N-containing heterocyclyl, aminosulfonyl, (6-membered N-containing heterocyclyl)sulfonyl, C₁-C₂-haloalkylcarbonylamino-sulfonyl and (optionally substituted phenyl)aminosulfonyl, and 30 6-membered nitrogen-containing heterocyclyl substituted with one or more substituents independently selected from pyridyl, phenyl,

C₁-C₄ alkyl, C₁-C₂ haloalkyl, C₁-C₂ alkoxy, amino, halo, piperidinyl, morpholinyl, C₁-C₂ alkylpiperazinyl, C₁-C₃ alkylaminothiocarbonyl, N,N-di-C₁-C₂.alkylamino-C₁-C₄-alkylenyl, N-C₁-C₂.alkylamino-C₁-C₄-alkylenyl, morpholinyl-C₁-C₄-alkylenylaminocarbonyl, aminocarbonyl, C₁-C₂-haloalkylcarbonylamino, morpholinyl-C₁-C₄-alkylenylamino, N,N-di-C₁-C₂-alkylamino and N,N-di-C₁-C₂.alkylamino-C₁-C₄-alkylenylamino,
5 preferably 3-(N,N-dimethylamino)-1-propynyl, 3-fluorophenyl, 4-fluorophenyl, 4-(N,N-dimethylamino)phenyl, 3-(methylcarbonylamino)phenyl, phenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 4-aminophenyl, 3-aminophenyl, 4-aminosulfonylphenyl, 4-(4-morpholinylsulfonyl)phenyl, 4-(trifluoroacetylaminosulfonyl)phenyl, 4-(trifluoromethylcarbonylaminosulfonyl)phenyl, 4-[(4-chlorophenyl)aminosulfonyl]phenyl, 3-(phenylsulfonylamino)phenyl, 2,4-difluorophenyl, 2,4-dimethoxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 3-ethoxyphenyl, 3,4-dimethoxyphenyl, 4-methylthiophenyl, 4-cyanophenyl, 4-trifluoromethoxyphenyl, 4-methoxyphenyl, 3-nitrophenyl, 3-methoxyphenyl, 2-methoxyphenyl, 2-thiazolyl, 2-pyrazinyl, 5-pyrimidinyl, 4-methyl-1-piperazinyl, 4-morpholinyl, 6-methoxy-3-pyridyl, 2-methoxy-3-pyridyl, 2-ethoxy-3-pyridyl, 3,4-dichloro-4-pyridyl, 6-(trifluoromethylcarbonylamino)-3-pyridyl, 6-amino-3-pyridyl, 3,5-dichloro-4-pyridyl, 2-chloro-4-pyridyl, 3-pyridyl and 4-pyridyl,
10 25 30 more preferably 5-pyrimidinyl, 2-pyrazinyl, morpholinyl, 4-methylpiperazinyl, 4-fluorophenyl, 4-(N,N-dimethylamino)propynyl, 3-nitrophenyl, 3-aminophenyl,

4-aminosulfonylphenyl, 3-aminosulfonylphenyl, 3-(phenylsulfonylamino)phenyl, 3-(methylcarbonylamino)phenyl, 4-[(trifluoromethylcarbonyl)aminosulfonyl]phenyl, 4-5 hydroxyphenyl, 4-methoxyphenyl, 2-thiazolyl, 6-(trifluoromethylcarbonylamino)-3-pyridyl, 6-amino-3-pyridyl, 3-pyridyl and 4-pyridyl;

and pharmaceutically acceptable salts thereof.

10 The invention also relates to compounds of Formula IV



wherein X¹ is CR¹ or N; wherein X² is CR¹ or N; wherein X³ is CH or N; provided only one of X¹, X² and X³ can be N; 15 preferably X¹ is CR¹; X² is CR¹; X³ is CH; provided X² is CH when X¹ is not CH;

wherein R¹ is one or more substituents selected from H, 20 optionally substituted pyrrolidinyl, optionally substituted piperazinyl, optionally substituted piperidinyl, morpholinyl, 1,4-dioxa-8-aza-spiro[4.5]decyl, pyridyl, phenyl, C₁-C₆-alkyl, C₁-C₂-haloalkyl, C₁-C₄-hydroxyalkyl, amino, C₁-C₄-azidoalkyl, C₁-C₄-cyanoalkyl, C₁-C₄-aminoalkyl, halo, hydroxy, 25 (optionally substituted pyrrolidinyl)-C₁-C₂-alkyl, (optionally substituted piperidinyl)-C₁-C₂-alkyl, (optionally substituted piperazinyl)-C₁-C₂-alkyl, morpholinyl-C₁-C₂-alkyl, (optionally substituted imidazolyl)-C₁-C₂-alkyl, phthalimidyl-C₁-C₂-alkyl, 30 optionally substituted azepanyl-C₁-C₂-alkyl, 1,4-dioxa-8-aza-spiro[4.5]decyl-C₁-C₂-alkyl, optionally substituted

phenoxy-C₁-C₂-alkyl, C₁-C₄-alkylaminothiocarbonyl, C₁-C₄-alkoxy-C₁-C₄-alkyl, C₁-C₄-alkylamino-C₁-C₄-alkyl, C₁-C₄-hydroxyalkylamino-C₁-C₄-alkyl, amino-C₁-C₄-alkoxy-C₁-C₄-alkyl, (1-aza-bicyclo[2.2.2]oct-3-yl)-oxy, optionally 5 substituted pyrrolidinyl-C₁-C₄-alkoxy, optionally substituted azetidinyl-C₁-C₄-alkoxy, optionally substituted piperidinyl-C₁-C₄-alkoxy, C₁-C₄-alkylamino-C₁-C₄-alkoxy, tetrahydrofuryl-O-, tetrahydrofuryl-C₁-C₄-alkoxy, optionally substituted pyridyloxy, optionally 10 substituted phenoxy, C₁-C₄-alkoxycarbonyl, 5-6-membered heterocyclyl-C₁-C₄-alkylaminocarbonyl, 5-6-membered N-containing heterocyclylcarbonyl, C₁-C₄-alkylaminocarbonyl, C₁-C₄-alkylamino-C₁-C₄-alkylaminocarbonyl, aminocarbonyl, 15 5-6-membered N-containing heterocyclyl-C₁-C₄-alkylamino, C₁-C₄-alkylamino-C₁-C₄-alkylamino-C₁-C₄-alkyl, and C₁-C₄-alkylamino-C₁-C₄-alkylamino, preferably methyl, ethyl, propyl, 1-methyl-4-piperazinyl, 1-benzyl-4-piperazinyl, 1-(2-pyrimidinyl)-4-piperazinyl, 1-(2-pyridyl)-4-piperazinyl, 1-ethyl-4-piperazinyl, 1-piperidinyl-CH₂-, 4-methyl-1-piperidinyl-CH₂-, 3-methyl-1-piperidinyl-CH₂-, 2-methyl-1-piperidinyl-CH₂-, 3,5-dimethyl-1-piperidinyl-CH₂-, 4-oxo-1-piperidinyl-CH₂-, 20 4-hydroxy-1-piperidinyl-CH₂-, 3-hydroxy-1-piperidinyl-CH₂-, 2-ethoxycarbonyl-1-piperidinyl-CH₂-, 3-ethoxycarbonyl-1-piperidinyl-CH₂-, 3-carboxy-1-piperidinyl-CH₂-, 4-ethoxycarbonyl-1-piperidinyl-CH₂-, 4-carboxy-1-piperidinyl-CH₂-, 4-(1-pyrrolidinyl)-1-piperidinyl-CH₂-, 4-(N-hydroxyethylamino)-1-piperidinyl-CH₂-, 4-(N-propylamino)-1-piperidinyl-CH₂-, 30 3-(N,N-diethylamino)carbonyl-1-piperidinyl-CH₂-, 4-morpholinyl-CH₂-, N,N-dimethylaminomethylenyl, N,N-diethylaminomethylenyl, N-methylaminomethylenyl, N-ethylaminomethylenyl and N,N-diethylamino, and

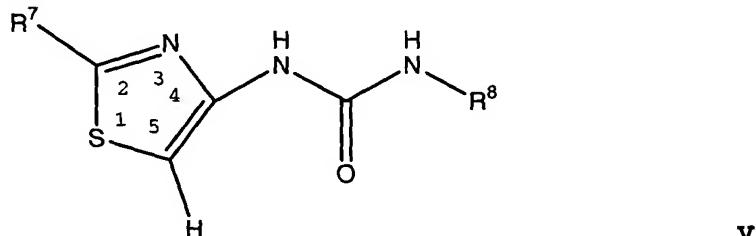
more preferably ethyl, propyl and 1-methyl-4-piperazinyl; and

wherein R² is halo, C₁-C₄-alkyl, C₁-C₄-alkylamino-C₂-C₄-alkynyl, C₃-C₆-cycloalkyl, optionally substituted 5
5 benzodioxolyl, optionally substituted indolyl, optionally substituted phenoxy, 5-membered oxygen or sulfur containing heteroaryl, 5- or 6-membered nitrogen-containing heterocyclyl, phenyl optionally substituted with one or two substituents selected

10 from halo, C₁-C₄-alkylamino, amino, C₁-C₄-alkoxy, C₁-C₂-haloalkyl, hydroxy, C₁-C₄-alkylthio, cyano, C₁-C₂-haloalkyloxy, aminosulfonyl, (6-membered N-
containing heterocyclyl)sulfonyl, C₁-C₂-haloalkylcarbonylaminosulfonyl, and (optionally
15 substituted phenyl)aminosulfonyl, and 6-membered nitrogen-containing heterocyclyl substituted with one or more substituents
independently selected from pyridyl, phenyl, C₁-C₄ alkyl, C₁-C₂ haloalkyl, C₁-C₂ alkoxy, halo,
20 piperidinyl, morpholinyl, C₁-C₂ alkylpiperazinyl, C₁-C₃ alkylaminothiocarbonyl, N,N-di-C₁-C₂-alkylamino-C₁-C₄-alkylenyl, N-C₁-C₂-alkylamino-C₁-C₄-alkylenyl, morpholinyl-C₁-C₄-alkylenylaminocarbonyl,
aminocarbonyl, morpholinyl-C₁-C₄-alkylenylamino,
25 N,N-di-C₁-C₂-alkylamino and N,N-di-C₁-C₂-alkylamino-C₁-C₄-alkylenylamino,
preferably 3-fluorophenyl, 4-fluorophenyl, 4-(N,N-dimethylamino)phenyl, 3-(methylcarbonylamino)phenyl,
phenyl, 3-trifluoromethylphenyl, 4-
30 trifluoromethylphenyl, 4-aminophenyl, 3-aminophenyl, 4-aminosulfonylphenyl, 4-(4-morpholinylsulfonyl)phenyl, 4-(trifluoroacetylaminosulfonyl)phenyl, 4-(trifluoromethylcarbonylaminosulfonyl)phenyl, 4-[(4-

chlorophenyl)aminosulfonyl]phenyl, 3-
 (phenylsulfonylamino)phenyl, 2,4-difluorophenyl, 2,4-
 dimethoxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 3-
 ethoxyphenyl, 3,4-dimethoxyphenyl, 4-
 5 methylthiophenyl, 4-cyanophenyl, 4-
 trifluoromethoxyphenyl, 4-methoxyphenyl, 3-
 nitrophenyl, 3-methoxyphenyl, 2-methoxyphenyl, 2-
 thiazolyl, 2-pyrazinyl, 5-pyrimidinyl, 4-methyl-1-
 piperazinyl, 4-morpholinyl, 6-methoxy-3-pyridyl, 2-
 10 methoxy-3-pyridyl, 2-ethoxy-3-pyridyl, 3,4-dichloro-
 4-pyridyl, 6-(trifluoromethylcarbonylamino)-3-
 pyridyl, 6-amino-3-pyridyl, 3,5-dichloro-4-pyridyl,
 2-chloro-4-pyridyl, 3-pyridyl and 4-pyridyl, and
 more preferably 4-pyridyl;
 15 and pharmaceutically acceptable salts thereof.

The invention also relates to compounds of Formula V



wherein R⁷ is selected from halo, C₁-C₄-alkyl, C₃-C₆-
 20 cycloalkyl, optionally substituted benzodioxolyl,
 optionally substituted indolyl, optionally substituted
 phenoxy, 5-membered oxygen or sulfur containing
 heteroaryl, 6-membered nitrogen-containing heterocyclyl,
 phenyl optionally substituted with one or two
 25 substituents selected
 from halo, C₁-C₄-alkylamino, amino, C₁-C₄-alkoxy, C₁-
 C₂-haloalkyl, hydroxy, C₁-C₄-alkylthio, cyano, C₁-C₂-
 haloalkyloxy, aminosulfonyl, (6-membered N-
 containing heterocyclyl)sulfonyl, C₁-C₂-

haloalkylcarbonylaminosulfonyl, and (optionally substituted phenyl)aminosulfonyl, and 6-membered nitrogen-containing heterocyclyl substituted with one or more substituents

5 independently selected from pyridyl, phenyl, C₁-C₄ alkyl, C₁-C₂ haloalkyl, C₁-C₂ alkoxy, halo, piperidinyl, morpholinyl, C₁-C₂ alkylpiperazinyl, C₁-C₃ alkylaminothiocarbonyl, N,N-di-C₁-C₂.alkylamino-C₁-C₄-alkylenyl, N-C₁-C₂.alkylamino-C₁-C₄-alkylenyl, morpholinyl-C₁-C₄-alkylenylaminocarbonyl, aminocarbonyl, morpholinyl-C₁-C₄-alkylenylamino, N,N-di-C₁-C₂.alkylamino and N,N-di-C₁-C₂.alkylamino-C₁-C₄-alkylenylamino,

10 preferably halo, C₁-C₄-alkyl, C₃-C₆-cycloalkyl, optionally substituted pyrimidinyl, morpholinyl, optionally substituted piperidinyl, optionally substituted benzodioxolyl, optionally substituted indolyl, optionally substituted phenoxy, optionally substituted thienyl, phenyl optionally substituted with one or two substituents

15 selected from halo, C₁-C₄-alkylamino, Boc-amino, amino, C₁-C₄-alkoxy, C₁-C₂-haloalkyl, hydroxy, C₁-C₄-alkylthio, cyano, C₁-C₂-haloalkyloxy, aminosulfonyl, (6-membered N-containing heterocyclyl)sulfonyl, C₁-C₂-haloalkylcarbonylaminosulfonyl, and (optionally substituted phenyl)aminosulfonyl,

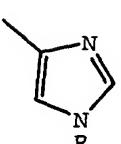
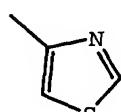
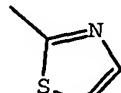
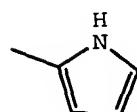
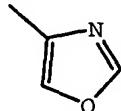
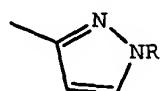
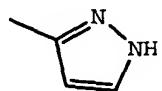
20 and pyridyl optionally substituted with one or two substituents selected from C₁-C₃ alkyl, C₁-C₄-alkoxy and halo,

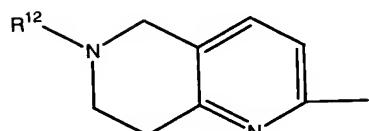
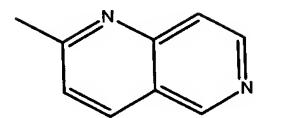
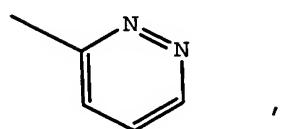
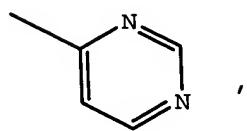
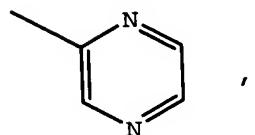
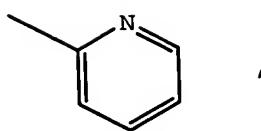
25 more preferably bromo, chloro, fluoro, C₁-C₃-alkyl, C₃-C₆-cycloalkyl, optionally substituted pyrimidinyl, morpholinyl, piperidinyl,

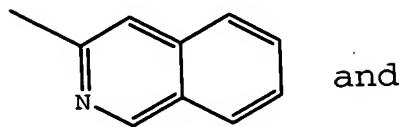
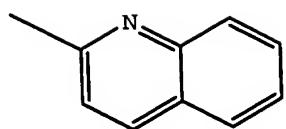
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benzodioxolyl, indolyl, phenoxy, thienyl,
phenyl optionally
substituted with one or two substituents
selected from fluoro, N,N-dimethylamino,
5 amino, methoxy, trifluoromethyl, Boc-amino,
hydroxy, ethoxy, methylthio, cyano,
trifluoromethoxy, aminosulfonyl, 4-
morpholinylsulfonyl,
trifluoroacetylaminosulfonyl, and (4-
10 chlorophenyl)aminosulfonyl,
and pyridyl optionally substituted with one or
two substituents selected from C₁-C₃ alkyl,
methoxy, ethoxy and chloro,
even more preferably bromo, methyl, ethyl,
15 cyclopropyl, cyclohexyl, 3-fluorophenyl, 4-
fluorophenyl, 4-(N,N-dimethylamino)phenyl,
phenyl, 3-trifluoromethylphenyl, 4-
trifluoromethylphenyl, 4-aminophenyl, 3-
aminophenyl, 4-Boc-aminophenyl, 4-
20 aminosulfonylphenyl, 4-(4-
morpholinylsulfonyl)phenyl, 4-
(trifluoroacetylaminosulfonyl)phenyl, 4-[(4-
chlorophenyl)aminosulfonyl]phenyl, 2,4-
difluorophenyl, 5-benzodioxolyl, 2,4-
25 dimethoxyphenyl, 3-hydroxyphenyl, 3-
ethoxyphenyl, 3,4-dimethoxyphenyl, 4-
methylthiophenyl, 5-indolyl, 4-cyanophenyl,
4-trifluoromethoxyphenyl, 4-methoxyphenyl,
3-methoxyphenyl, 2-methoxyphenyl, phenoxy,
30 2-thienyl, 4-pyrimidinyl, 2-methylthio-4-
pyrimidinyl, morpholinyl, 4-piperidinyl, 6-
methoxy-3-pyridyl, 2-methoxy-3-pyridyl, 2-
ethoxy-3-pyridyl, 3,4-dichloro-4-pyridyl,

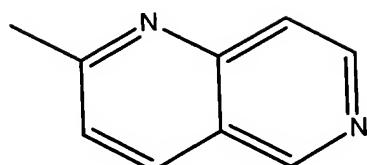
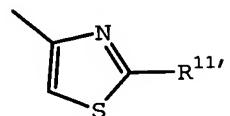
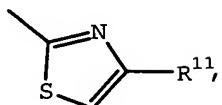
3,5-dichloro-4-pyridyl, 2-chloro-4-pyridyl,
3-pyridyl and 4-pyridyl; and
wherein R⁸ is selected from

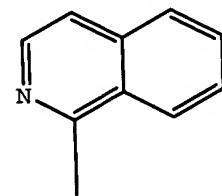
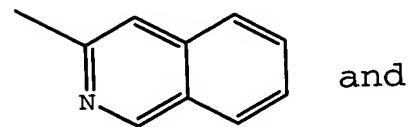
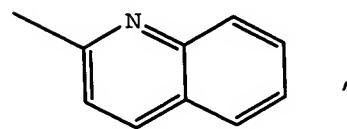
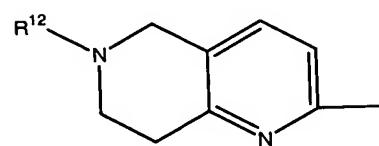
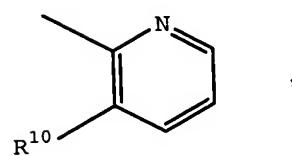
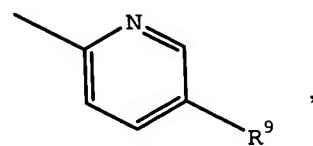
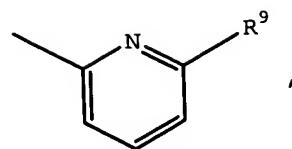


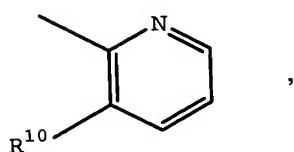
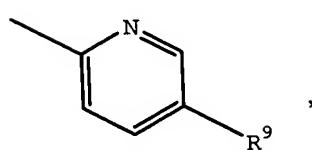
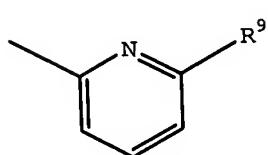
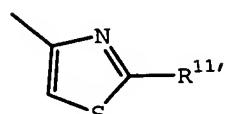
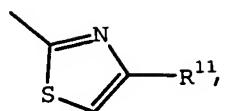




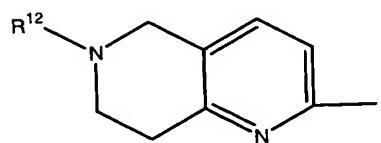
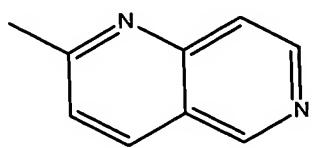
preferably

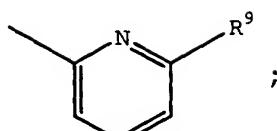
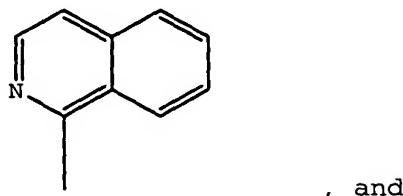
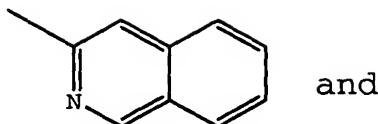






5





even more preferably

wherein R⁸ is optionally substituted with one or two
 substituents independently selected from H, optionally
 5 substituted pyrrolidinyl, optionally substituted
 piperazinyl, optionally substituted piperidinyl,
 morpholinyl, 1,4-dioxa-8-aza-spiro[4.5]decyl, pyridyl,
 phenyl, C₁-C₆-alkyl, C₁-C₂-haloalkyl, C₁-C₄-hydroxyalkyl,
 amino, C₁-C₄-azidoalkyl, C₁-C₄-cyanoalkyl, C₁-C₄-
 10 aminoalkyl, halo, hydroxy, ((optionally substituted
 pyrrolidinyl)-C₁-C₂-alkyl, (optionally substituted
 piperidinyl)-C₁-C₂-alkyl, (optionally substituted
 piperazinyl)-C₁-C₂-alkyl, morpholinyl-C₁-C₂-alkyl,
 (optionally substituted imidazolyl)-C₁-C₂-alkyl,
 15 phthalimidyl-C₁-C₂-alkyl, optionally substituted
 azepanyl-C₁-C₂-alkyl, 1,4-dioxa-8-aza-spiro[4.5]decyl-C₁-
 C₂-alkyl, optionally substituted phenoxy-C₁-C₂-alkyl, C₁-
 C₄-alkylaminothiocarbonyl, C₁-C₄-alkoxy-C₁-C₄-alkyl, C₁-
 C₄-alkylamino-C₁-C₄-alkyl, C₁-C₄-hydroxyalkylamino-C₁-C₄-
 20 alkyl, amino-C₁-C₄-alkoxy-C₁-C₄-alkyl, (1-aza-
 bicyclo[2.2.2]oct-3-yl)-oxy, optionally substituted
 pyrrolidinyl-C₁-C₄-alkoxy, optionally substituted
 azetidinyl-C₁-C₄-alkoxy, optionally substituted

5 piperidinyl-C₁-C₄-alkoxy, C₁-C₄-alkylamino-C₁-C₄-alkoxy,
 tetrahydrofuryl-O-, tetrahydrofuryl-C₁-C₄-alkoxy,
 optionally substituted pyridyloxy, optionally
 substituted phenoxy, C₁-C₄-alkoxycarbonyl, 5-6-membered
 heterocyclyl-C₁-C₄-alkylaminocarbonyl, 5-6-membered N-
 containing heterocyclylcarbonyl, C₁-C₄-
 alkylaminocarbonyl, C₁-C₄-alkylamino-C₁-C₄-
 alkylaminocarbonyl, aminocarbonyl, 5-6-membered N-
 containing heterocyclyl-C₁-C₄-alkylamino, C₁-C₄-
10 alkylamino, C₁-C₄-alkylamino-C₁-C₄-alkylamino-C₁-C₄-alkyl,
 and C₁-C₄-alkylamino-C₁-C₄-alkylamino,
 preferably unsubstituted or substituted with one or
 more substituents selected from pyridyl, phenyl, C₁-
 C₄ alkyl, C₁-C₂ haloalkyl, halo, piperidinyl,
15 morpholinyl, methylpiperazinyl,
 methylaminothiocarbonyl, N,N-
 diethylaminomethylene, N-methylaminomethylene,
 morpholinylpropenylaminocarbonyl, aminocarbonyl
 morpholinylpropenylamino, N,N-diethylamino and
20 N,N-dimethylaminoethylenylamino;

wherein R⁹ is selected from optionally substituted
25 pyrrolidinyl, optionally substituted piperazinyl,
 optionally substituted piperidinyl, morpholinyl, 1,4-
 dioxa-8-aza-spiro[4.5]decyl, pyridyl, phenyl, C₁-C₄ alkyl,
 C₁-C₂ haloalkyl, C₁-C₂ hydroxyalkyl, amino, C₁-C₂
 azidoalkyl, C₁-C₂ cyanoalkyl, C₁-C₂ aminoalkyl, halo,
 (optionally substituted pyrrolidinyl)CH₂-, (optionally
 substituted piperidinyl)-CH₂-, (optionally substituted
 piperazinyl)-CH₂-, 4-morpholinyl-CH₂-, (optionally
30 substituted imidazolyl)-CH₂-, phthalimidylethyl,
 optionally substituted azepanyl-CH₂-, 1,4-dioxa-8-aza-
 spiro[4.5]decyl-CH₂-, optionally substituted phenoxy-CH₂-,
 C₁-C₄-alkylaminothiocarbonyl, C₁-C₄-alkoxy-C₁-C₄-alkyl, C₁-
 C₄-alkylamino-C₁-C₄-alkyl, C₁-C₄-hydroxyalkylamino-C₁-C₄-

alkyl, Boc-aminoethoxymethylenyl, amino-C₁-C₄-alkoxy-C₁-C₄-alkyl, (1-aza-bicyclo[2.2.2]oct-3-yl)-oxy, optionally substituted pyrrolidinyl-C₁-C₄-alkoxy, optionally substituted azetidinyl-C₁-C₄-alkoxy, optionally substituted piperidinyl-C₁-C₄-alkoxy, C₁-C₄-alkylamino-C₁-C₄-alkoxy, tetrahydrafuryl-O-, tetrahydrafuryl-C₁-C₄-alkoxy, optionally substituted phenoxy, C₁-C₄-alkoxycarbonyl, heterocyclyl-C₁-C₄-alkylaminocarbonyl, 1-piperidinylcarbonyl, C₁-C₄-alkylaminocarbonyl, C₁-C₄-alkylamino-C₁-C₄-alkylaminocarbonyl, aminocarbonyl, morpholinyl-C₁-C₄-alkylamino, C₁-C₄-alkylamino, C₁-C₄-alkylamino-C₁-C₄-alkylamino-C₁-C₄-alkyl, and C₁-C₄-alkylamino-C₁-C₄-alkylamino,

10 preferably 3-(N,N-dimethylamino)-1-pyrrolidinyl, 1-methyl-4-piperazinyl, 1-benzyl-4-piperazinyl, 1-(2-pyrimidinyl)-4-piperazinyl, 1-(2-pyridyl)-4-piperazinyl, 1-ethyl-4-piperazinyl, 4-amino-1-piperidinyl, 4-(N-hydroxyethylamino)-1-piperidinyl, 4-(N-propylamino)-1-piperidinyl, 4-(N-benzylamino)-1-piperidinyl, 4-oxo-piperidinyl, 4-(hydroxyimino)-piperidinyl, 4-morpholinyl, 1,4-dioxa-8-aza-spiro[4.5]decyl, pyridyl, phenyl, methyl, ethyl, propyl, amino, azidomethyl, hydroxymethyl, trifluoromethyl, fluoro, chloro, bromo, aminoethyl, aminomethyl, cyanomethyl, 1-pyrrolidinyl-CH₂-, 2-methoxycarbonyl-1-pyrrolidinyl-CH₂-, 2-carboxy-1-pyrrolidinyl-CH₂-, 2-hydroxymethyl-1-pyrrolidinyl-CH₂-, 1-piperidinyl-CH₂-, 4-methyl-1-piperidinyl-CH₂-, 3-methyl-1-piperidinyl-CH₂-, 2-methyl-1-piperidinyl-CH₂-, 30 3,5-dimethyl-1-piperidinyl-CH₂-, 4-oxo-1-piperidinyl-CH₂-, 4-hydroxy-1-piperidinyl-CH₂-, 3-hydroxy-1-piperidinyl-CH₂-, 2-ethoxycarbonyl-1-piperidinyl-CH₂-, 3-ethoxycarbonyl-1-piperidinyl-CH₂-, 3-carboxy-1-piperidinyl-CH₂-, 4-ethoxycarbonyl-1-piperidinyl-CH₂-,

4-carboxy-1-piperidinyl-CH₂-, 4-(1-pyrrolidinyl)-1-piperidinyl-CH₂-, 4-(N-hydroxyethylamino)-1-piperidinyl-CH₂-, 4-(N-propylamino)-1-piperidinyl-CH₂-, 1-methyl-4-piperazinyl-CH₂-, 4-morpholinyl-CH₂-, (2-methyl-1-imidazolyl-CH₂-, 3-(N,N-diethylamino)carbonyl-1-piperidinyl-CH₂-, phthalimidylethyleneyl, 1-azepanyl-CH₂-, 1,4-dioxa-8-aza-spiro[4.5]decyl-CH₂-, 4-(methyl)phenoxyethyleneyl, 4-(N,N-dimethylaminomethyleneyl)phenoxyethyleneyl,
10 methylaminothiocarbonyl, methoxymethyleneyl, ethylaminothiocarbonyl, N,N-dimethylaminoethyleneyl, N,N-diethylaminomethyleneyl, N-methylaminomethyleneyl, N-(hydroxypropyl)aminomethyleneyl, N-ethylaminomethyleneyl, Boc-aminoethoxymethyleneyl, aminoethoxymethyleneyl, (1-aza-bicyclo[2.2.2]oct-3-yl)-oxy, 2-pyrrolidinylmethoxy, 1-methyl-2-pyrrolidinylmethoxy, azetidin-3-ylmethoxy, N-Boc-azetidin-3-ylmethoxy, N-Boc-piperidin-4-ylethoxy, 1-methyl-4-piperidinylethoxy, 4-piperidinylethoxy, 4-piperidinylmethoxy, N,N-dimethylaminoethoxy, 3-tetrahydrofuryl-O-, 3-tetrahydrofurylmethoxy, 4-tetrahydrofurylmethoxy, 4-methylphenoxy, 4-(aminoethyl)phenoxy, 4-(1-imidazolyl)phenoxy, 2,4-dimethylphenoxy, phenoxy, 4-cyanophenoxy, 4-[1,3]dioxolan-2-ylphenoxy, 4-fluorophenoxy, 3,4-difluorophenoxy, ethoxycarbonyl, morpholinylpropylenylaminocarbonyl, 1-piperidinylcarbonyl, methylaminocarbonyl, ethylaminocarbonyl, N,N-diethylaminocarbonyl, N-(N',N'-dimethylaminoethyleneyl)aminocarbonyl, aminocarbonyl, morpholinylpropylenylamino, N,N-diethylamino(2-propylenyl)aminomethyleneyl, N,N-diethylamino(1-

propylenyl)aminomethylenyl and N-(N',N'-dimethylaminoethylenyl)amino;

wherein R¹⁰ is selected from H, hydroxy, and amino;

wherein R¹¹ is selected from pyridyl and pyrimidinyl,

5 preferably pyridyl; and

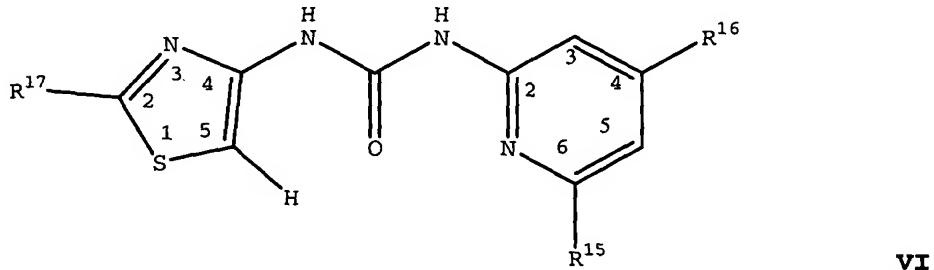
wherein R¹² is selected from H, and C₁-C₄ alkyl,

preferably H, methyl, ethyl and propyl;

and pharmaceutically acceptable salts thereof.

The invention also relates to compounds of Formula VI

10



wherein R¹⁵ is one or more substituents selected from H, optionally substituted heterocyclyl, phenyl, C₁-C₆-alkyl,

15 C₁-C₂-haloalkyl, C₁-C₄-hydroxyalkyl, amino, C₁-C₄-azidoalkyl, C₁-C₄-cyanoalkyl, C₁-C₄-aminoalkyl, halo, hydroxy, (optionally substituted heterocyclyl)-C₁-C₄-alkyl, optionally substituted phenoxy-C₁-C₂-alkyl, C₁-C₄-alkoxy-C₁-C₄-alkyl, C₁-C₄-alkylamino-C₁-C₄-alkyl, C₁-C₄-hydroxyalkylamino, amino-C₁-C₄-alkoxy-C₁-C₄-alkyl, 20 optionally substituted heterocyclyloxy, optionally substituted heterocyclyl-C₁-C₄-alkoxy, C₁-C₄-alkylamino-C₁-C₄-alkoxy, optionally substituted phenoxy, C₁-C₄-alkoxycarbonyl, 5-6-membered heterocyclyl-C₁-C₄-alkylaminocarbonyl, 5-6-membered N-containing heterocyclylcarbonyl, C₁-C₄-alkylaminocarbonyl, C₁-C₄-alkylaminothiocarbonyl, C₁-C₄-alkylamino-C₁-C₄-alkylaminocarbonyl, aminocarbonyl, 25 5-6-membered N-containing heterocyclyl-sulfonyl-C₁-C₄-alkyl, 5-6-membered

N-containing heterocycl- C_1 - C_4 -alkylamino, C_1 - C_4 -alkylamino, C_1 - C_4 -alkylamino- C_1 - C_4 -alkylamino- C_1 - C_4 -alkyl, and C_1 - C_4 -alkylamino- C_1 - C_4 -alkylamino; preferably H, optionally substituted pyrrolidinyl, 5 optionally substituted piperazinyl, optionally substituted piperidinyl, morpholinyl, 1,2,3,6-tetrahydro-pyridinyl, (optionally substituted pyrrolidinyl)- C_1 - C_2 -alkyl, (optionally substituted piperidinyl)- C_1 - C_2 -alkyl, (optionally substituted piperazinyl)- C_1 - C_2 -alkyl, morpholinyl- C_1 - C_2 -alkyl, C_1 - C_4 -alkylamino- C_1 - C_4 -alkyl, C_1 - C_4 -hydroxyalkylamino, 10 (optionally substituted pyrrolidinyl)- C_1 - C_2 -alkylamino, (optionally substituted piperidinyl)- C_1 - C_2 -alkylamino, (optionally substituted piperazinyl)- C_1 - C_2 -alkylamino, morpholinyl- C_1 - C_2 -alkylamino, 15 optionally substituted pyrrolidinyl- C_1 - C_4 -alkoxy, optionally substituted azetidinyl- C_1 - C_4 -alkoxy, tetrahydrofuryl- C_1 - C_4 -alkoxy, optionally substituted piperidinyl- C_1 - C_4 -alkoxy, C_1 - C_4 -alkylamino- C_1 - C_4 -alkoxy, tetrahydrofuryloxy, 20 optionally substituted piperidinyloxy, optionally substituted phenoxy, C_1 - C_4 -alkylaminocarbonyl and C_1 - C_4 -alkylaminothiocarbonyl; more preferably H, tetrahydro-furanyloxy, 1- 25 methylpyrrolidin-2-ylmethoxy, 2-pyrrolidinylmethoxy, 3-pyrrolidinylmethoxy, 1-Boc-pyrrolidin-2-ylmethoxy, 4-piperidinylmethoxy, 1-Boc-piperidin-4-ylmethoxy, 1-Boc-piperidin-4-yloxy, piperidin-4-yloxy, 1-methyl-piperidin-4-ylmethoxy, 1-Boc-azetidin-3-ylmethoxy, 1-methyl-azetidin-3-ylmethoxy, 3-azetidinylmethoxy, 1-methyl-piperidin-4-yloxy, 30 phenoxy, 4-(pyrrolidin-1-ylmethyl)phenoxy, dimethylaminoethoxy, piperidinylethylamino, 1-piperidinylmethyl, 1-(piperidin-1-yl)ethyl, 3-methylpiperidin-1-ylmethyl, 1-pyrrolidinylmethyl,

2,2,6,6-tetramethylpiperidin-1-ylmethyl, 2,6-dimethylpiperidin-1-ylmethyl, dimethylaminomethyl, diethylaminomethyl, diethylaminothiocarbonyl, diethylaminocarbonyl, N-Boc-N-isopropylaminomethyl, isopropylaminomethyl, 2-thienylsulfonylmethyl, hydroxypropylamino, 4-ethyl-piperidin-1-yl, 4-(2-pyridyl)piperidin-1-yl, 1-methylpiperidin-4-yl, 4-(2-pyrazinyl)piperidin-1-yl, 1-methyl-1,2,3,6-tetrahydro-pyridin-4-yl, 1,2,3,6-tetrahydro-pyridin-4-yl, and 1-Boc-1,2,3,6-tetrahydro-pyridin-4-yl;

wherein R¹⁶ is selected from H, heterocyclylcarbonyl, alkylaminocarbonyl, alkylaminomethyl, and heterocyclylmethyl;

preferably H, 5-6-membered nitrogen containing heterocyclylcarbonyl, C₁-C₄-alkylaminocarbonyl, C₁-C₄-alkylaminomethyl, and 5-6-membered nitrogen containing heterocyclylmethyl;

more preferably H, 1-piperidinylcarbonyl, diethylaminocarbonyl, diethylaminomethyl, 1-piperidinylmethyl; and

wherein R¹⁷ is selected from halo, and preferably chloro and bromo, C₁-C₃-alkyl, preferably C₁-C₂-alkyl, and more preferably methyl,

cycloalkylalkynyl, preferably C₃-C₆-cycloalkyl-C₂-C₄-alkynyl, and more preferably cyclopropylethynyl, cycloalkyl, preferably C₃-C₆-cycloalkyl, and more preferably cyclopropyl, optionally substituted heteroarylsulfonyl-C₁-C₄-alkyl, and preferably optionally substituted 5-6-membered heteroarylsulfonyl-C₁-C₂-alkyl, optionally substituted indolyl, and preferably 1-Boc-indol-5-yl, optionally substituted phenoxy,

optionally substituted indazolyl, and preferably 5-indazolyl,
unsubstituted 5-membered oxygen or sulfur containing heteroaryl, and preferably unsubstituted thiienyl,
5 and 5-tert-butyloxazol-2-yl,
unsubstituted 6-membered nitrogen-containing heterocyclyl,
phenyl optionally substituted with one or two substituents selected from halo, C₁-C₄-alkylamino, amino, nitro, C₁-C₄-alkoxy, C₁-C₂-haloalkyl, hydroxy, C₁-C₄-alkylthio, C₁-C₄-alkylcarbonylamino, (optionally substituted phenyl)sulfonylamino, cyano, C₁-C₂-haloalkoxy, 5- or 6-membered N-containing heterocyclyl,
15 aminosulfonyl, (6-membered N-containing heterocyclyl)sulfonyl, C₁-C₂-haloalkylcarbonylaminosulfonyl and (optionally substituted phenyl)aminosulfonyl, and
preferably optionally substituted with one or two
20 substituents selected from halo, C₁-C₄-alkylamino, amino, nitro, C₁-C₄-alkoxy, C₁-C₂-haloalkyl, hydroxy, C₁-C₄-alkylthio, C₁-C₄-alkylcarbonylamino, (optionally substituted phenyl)sulfonylamino, cyano, C₁-C₂-haloalkoxy,
25 5- or 6-membered N-containing heterocyclyl, aminosulfonyl, (6-membered N-containing heterocyclyl)sulfonyl, C₁-C₂-haloalkylcarbonylaminosulfonyl and (optionally substituted phenyl)aminosulfonyl; and more
30 preferably and phenyl optionally substituted with aminosulfonyl, and
6-membered nitrogen-containing heterocyclyl substituted with one or more substituents independently selected from pyridyl, phenyl, C₁-

1-(2-Chloro-thiazol-4-yl)-3-[4-(piperidine-1-carbonyl)-
pyridin-2-yl]-urea;

N,N-Diethyl-2-[3-(2-pyridin-4-yl-thiazol-4-yl)-ureido]-
isonicotinamide;

5 N,N-Diethyl-2-[3-(2-phenyl-thiazol-4-yl)-ureido]-
isonicotinamide;

2-[3-(2-Bromo-thiazol-4-yl)-ureido]-N,N-diethyl-
isonicotinamide;

1-(4-Diethylaminomethyl-pyridin-2-yl)-3-(2-pyridin-4-yl-
thiazol-4-yl)-urea;

10 1-[6-(2,6-Dimethyl-piperidin-1-ylmethyl)-pyridin-2-yl]-3-(2-
pyridin-4-yl-thiazol-4-yl)-urea;

1-[6-(1-Piperidin-1-yl-ethyl)-pyridin-2-yl]-3-(2-pyridin-4-
yl-thiazol-4-yl)-urea;

15 2-({6-[3-(2-Pyridin-4-yl-thiazol-4-yl)-ureido]-pyridin-2-
ylamino}-methyl)-piperidine-1-carboxylic acid tert-butyl
ester;

1-{6-[(Piperidin-2-ylmethyl)-amino]-pyridin-2-yl}-3-(2-
pyridin-4-yl-thiazol-4-yl)-urea;

20 (S)-1-[6-(3-Methyl-piperidin-1-ylmethyl)-pyridin-2-yl]-3-(2-
pyridin-4-yl-thiazol-4-yl)-urea;

(R)-1-[6-(3-Methyl-piperidin-1-ylmethyl)-pyridin-2-yl]-3-(2-
pyridin-4-yl-thiazol-4-yl)-urea;

1-(2-Chloro-thiazol-4-yl)-3-(6-piperidin-1-ylmethyl-pyridin-
2-yl)-urea;

25 1-(2-Bromo-thiazol-4-yl)-3-[6-(2-piperidin-4-yl-ethoxy)-
pyridin-2-yl]-urea;

1-(2-Chloro-thiazol-4-yl)-3-[6-(2-piperidin-4-yl-ethoxy)-
pyridin-2-yl]-urea;

30 1-[6-(Azetidin-3-ylmethoxy)-pyridin-2-yl]-3-(2-bromo-
thiazol-4-yl)-urea;

1-[6-(Azetidin-3-ylmethoxy)-pyridin-2-yl]-3-(2-chloro-
thiazol-4-yl)-urea;

1-(2-Bromo-thiazol-4-yl)-3-[6-(piperidin-4-ylmethoxy)-
pyridin-2-yl]-urea;
1-(2-Chloro-thiazol-4-yl)-3-[6-(piperidin-4-ylmethoxy)-
pyridin-2-yl]-urea;
5 3-[4-{3-[6-(1-Methyl-pyrrolidin-2-ylmethoxy)-pyridin-2-yl]-
ureido}-thiazol-2-yl]-benzenesulfonamide;
tert-Butyl 3-[6-[3-(2-pyridin-4-yl-thiazol-4-yl)-ureido]-
pyridin-2-ylloxymethyl]-pyrrolidine-1-carboxylate;
1-(2-Pyridin-4-yl-thiazol-4-yl)-3-[6-(pyrrolidin-3-
10 ylmethoxy)-pyridin-2-yl]-urea;
1-(2-Cyclopropyl-thiazol-4-yl)-3-[6-(2-piperidin-4-yl-
ethoxy)-pyridin-2-yl]-urea;
1-[6-(Isopropylamino-methyl)-pyridin-2-yl]-3-(2-pyridin-4-
yl-thiazol-4-yl)-urea;
15 Isopropyl-[6-[3-(2-phenyl-thiazol-4-yl)-ureido]-pyridin-2-
ylmethoxy]-carbamic acid tert-butyl ester;
1-[6-(Isopropylamino-methyl)-pyridin-2-yl]-3-(2-phenyl-
thiazol-4-yl)-urea;
1-(2-Bromo-thiazol-4-yl)-3-[6-(isopropylamino-methyl)-
20 pyridin-2-yl]-urea;
1-(2-Bromo-thiazol-4-yl)-3-[6-(1-methyl-pyrrolidin-2-
ylmethoxy)-pyridin-2-yl]-urea;
1-(2-Chloro-thiazol-4-yl)-3-[6-(1-methyl-pyrrolidin-2-
ylmethoxy)-pyridin-2-yl]-urea;
25 1-(2-phenylthiazol-4-yl)-3-(6-p-pyrrolidin-1-
ylmethoxyphenoxy)pyridin-2-yl)urea;
1-(2-Pyridin-4-yl-thiazol-4-yl)-3-[6-(tetrahydro-furan-3-
yloxy)-pyridin-2-yl]-urea;
1-[2-(1H-Indazol-5-yl)-thiazol-4-yl]-3-(6-piperidin-1-
30 ylmethyl-pyridin-2-yl)-urea;
1-(1'-Methyl-1',2',3',6'-tetrahydro-[2,4']bipyridinyl-6-yl)-
3-(2-pyridin-4-yl-thiazol-4-yl)-urea;

1-(2-Bromo-thizol-4-yl)-3-(1'-methyl-1',2',3',6'-tetrahydro-[2,4']bipyridinyl-6-yl)-urea;

1-(1'-Methyl-1',2',3',6'-tetrahydro-2[2,4]bipyridinyl-6-yl)-3-(2-phenyl-thiazol-4-yl)-urea;

5 1-[6-(3-Hydroxy-propylamino)-pyridin-2-yl]-3-(2-pyridin-4-yl-thizol-4-yl)-urea;

1-(2-Bromo-thiazol-4-yl)-3-[6(3-hydroxy-propylamino)-pyridin-2-yl]-urea;

1-(1'-Methyl-1',2',3',4',5',6'-hexahydro-[2,4']bipydrinyl-6-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)-urea;

10 1-(1'-Methyl-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl-6-yl)-3-(2-phenyl-thiazol-4-yl)-urea;

6-[3-(2-Pyridin-4-yl-thizol-4-yl)-ureido]-3',6'-dihydro-2'H-[2,4]bipyridinyl-1'-carboxylic acid tert-butylester;

15 1-(2-Pyridin-4-yl-thiazol-4-yl)-3-(1',2',3',6'-tetrahydro-[2,4']bipyridinyl-6-yl)-urea;

1-(2-Pyridin-4-yl-thizol-4-yl)-3-[6-(tetrahydro-furan-3-ylmethoxy)-pyridin-2-yl]-urea;

20 2-[6-[3-(2-Pyridin-4-yl-thiazol-4-yl)-ureido]-pyridin-2-yloxyethyl]-pyrrolidine-1-carboxylic acid tert-butyl ester;

1-(2-Pyridin-4-yl-thiazol-4-yl)-3-[6-(pyrrolidin-2-ylmethoxy)-pyridin-2-yl]-urea;

25 6-[3-(2-Pyridin-4-yl-thiazol-4-yl)-ureido]-pyridine-2-carbothioic acid diethylamide;

1-(2-Bromo-thiazol-4-yl)-3-[6-(3-methyl-piperidin-1-ylmethyl)-pyridin-2-yl]-urea;

1-(2-Chloro-thiazol-4-yl)-3-[6-(3-methyl-piperidin-1-ylmethyl)-pyridin-2-yl]-urea;

30 1-(2-Phenyl-thiazol-4-yl)-3-[4-(piperidine-1-carbonyl)-pyridin-2-yl]-urea;

1-(2-Bromo-thiazol-4-yl)-3-[4-(piperidine-1-carbonyl)-pyridin-2-yl]-urea;

1-[2-(2-Methoxy-pyridin-4-yl)-thiazol-4-yl]-3-(6-phenoxy-pyridin-2-yl)-urea;
1-[2-(2-Methoxy-pyridin-4-yl)-thiazol-4-yl]-3-[6-(1-methyl-pyrrolidin-2-ylmethoxy)-pyridin-2-yl]-urea;
5 1-[6-(2-Dimethylamino-ethoxy)-pyridin-2-yl]-3-[2-(2-methoxy-pyridin-4-yl)-thiazol-4-yl]-urea;
1-[6-(1-Methyl-pyrrolidin-2-ylmethoxy)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea;
1-(2-phenylthiazol-4-yl)-3-(6-pyrrolidin-1-ylmethyl-pyridin-2-yl)urea;
10 1-(6-Diethylaminomethylpyridin-2-yl)-3-(2-phenylthiazol-4-yl)urea;
(S)-1-[6-(1-Methylpyrrolidin-2-ylmethoxy)pyridin-2-yl]-3-(2-phenylthiazol-4-yl)urea;
15 1-[6-(2-Piperidin-4-yl-ethoxy)pyridin-2-yl]-3-[2-phenylthiazol-4-yl]urea;
1-[6-(4-Ethylpiperazin-1-yl)-pyridin-2-yl]-3-(2-phenylthiazol-4-yl)urea;
1-(2-phenylthiazol-4-yl)-3-[6-(4-pyrimidin-2-yl-piperazin-1-yl)pyridin-2-yl]urea;
20 Diethyl 6-[3-(2-phenylthiazol-4-yl)ureido]-pyridine-2-carboxamide;
1-(2-Pyridin-4-yl-thiazol-4-yl)-3-(6-p-pyrrolidin-1-ylmethoxyphenoxy)pyridin-2-yl)urea;
25 1-(2-Bromothiazol-4-yl)-3-(6-p-pyrrolidin-1-ylmethoxyphenoxy)pyridin-2-yl)urea;
1-[6-(Piperidin-4-ylmethoxy)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea;
1-[6-(1-Methyl-piperidin-4-ylmethoxy)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea;
30 1-[6-(1-Methyl-piperidin-4-yloxy)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea;
1-[6-(1-Methyl-azetidin-3-ylmethoxy)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea;

1-[6-(Azetidin-3-ylmethoxy)-pyridin-2-yl]-3-(2-phenyl-thiazol-4-yl)-urea;

1-[6-(1-Methyl-azetidin-3-ylmethoxy)-pyridin-2-yl]-3-(2-phenyl-thiazol-4-yl)-urea;

5 1-(2-Phenyl-thiazol-4-yl)-3-[6-(piperidin-4-ylmethoxy)-pyridin-2-yl]-urea;

1-[6-(1-Methyl-piperidin-4-ylmethoxy)-pyridin-2-yl]-3-(2-phenyl-thiazol-4-yl)-urea;

1-[6-(1-Methyl-piperidin-4-ylmethoxy)-pyridin-2-yl]-3-(2-phenyl-thiazol-4-yl)-urea;

10 1-[6-(2-Piperidin-4-yl-ethoxy)-pyridin-2-yl]-3-(2-thiophen-2-yl-thiazol-4-yl)-urea;

1-[6-(1-Methyl-pyrrolidin-2-ylmethoxy)-pyridin-2-yl]-3-[2-(thiophene-2-sulfonylmethyl)-thiazol-4-yl]-urea;

15 1-[2-(2-Methoxy-pyridin-4-yl)-thiazol-4-yl]-3-(6-piperdin-1-ylmethyl-pyridin-2-yl)-urea; and

[2-(2-Chloro-pyridin-4-yl)-thiazol-4-yl]-3-(6-piperdin-1-ylmethyl-pyridin-2-yl)-urea.

20 **Indications**

Compounds of the present invention would be useful for, but not limited to, the treatment of cell proliferative diseases or of apoptosis.

The compounds of the invention are endowed with kinase inhibitory activity, such as CDK/cyclin kinase inhibitory activity and GSK inhibitory activity.

The compounds of the invention are useful in therapy as antineoplasia agents.

Compounds of the invention would be useful for the treatment of neoplasia including cancer, including, but not limited to: carcinoma such as cancer of the bladder, breast, colon, kidney, liver, lung (including small cell lung cancer), esophagus, gall-bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin (including squamous cell carcinoma); hematopoietic tumors of lymphoid lineage

(including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell-Lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma and Burkett's lymphoma); hematopoietic tumors of 5 myeloid lineage (including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia); tumors of mesenchymal origin (including fibrosarcoma and rhabdomyosarcoma, and other sarcomas, e.g. soft tissue and bone); tumors of the central and peripheral 10 nervous system (including astrocytoma, neuroblastoma, glioma and schwannomas); and other tumors (including melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratoctanthoma, thyroid follicular cancer and Kaposi's sarcoma).

15 Preferably, the compounds are useful for the treatment of neoplasia selected from lung cancer, colon cancer and breast cancer.

Due to the key role of CDKs in the regulation of cellular proliferation, these compounds are also useful in 20 the treatment of a variety of cell proliferative disorders such as, for instance, blood vessel proliferative disorders including arthritis and restenosis; fibrotic disorders including hepatic cirrhosis and atherosclerosis; mesangial cell proliferative disorders including glomerulonephritis, 25 diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, transplant rejection and glomerulopathies; metabolic disorders including psoriasis, diabetes mellitus, chronic wound healing, inflammation, and diabetic retinopathy and other vision disorders; and others 30 including benign prostate hyperplasia, familial adenomatosis polyposis, neuro-fibromatosis, pulmonary fibrosis, angiogenesis, metastasis, vascular smooth cell proliferation, post-surgical stenosis and hypertrophic scar

formation, eczema, inflammatory bowel disease, endotoxic shock, and fungal infections.

The compounds of the invention are useful to prevent the phosphorylation of tau protein.

5 The compounds of the invention are useful in the treatment of neurological disorders, including neurological injuries and neurodegenerative diseases, such as, but not limited to, stroke, brain trauma, epilepsy, spinal cord injury, ischemia, multiple sclerosis, vision related 10 disorders including but not limited to glaucoma and macular degeneration, hearing loss, AIDS-related dementia, retinitis pigmentosa, spinal muscular atrophy, cerebellar degeneration, amyotrophic lateral sclerosis, Parkinson's disease, Huntington's disease and Alzheimer's disease.

15 Compounds of Formula I-VI, as inhibitors of the CDKs, can modulate the level of cellular RNA and DNA synthesis. These agents would therefore be useful in the treatment of viral infections, including but not limited to HIV, human papilloma virus, herpesvirus, poxvirus, Epstein-Barr virus, 20 Sindbis virus and adenovirus.

The compounds of this invention may also act as inhibitors of other protein kinases, e.g. KDR, IKK, JNK3, and thus be effective in the treatment of diseases associated with other protein kinases.

25 Besides being useful for human treatment, these compounds are also useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like. More preferred animals include horses, dogs, and cats.

30 Inhibitors of certain kinases may have utility in the treatment of diseases when the kinase is not misregulated, but is nonetheless essential for maintenance of the disease state. In this case, inhibition of the kinase activity would act either as a cure or palliative for these

diseases. For example, many viruses, such as human papilloma virus, disrupt the cell cycle and drive cells into the S-phase of the cell cycle. Preventing cells from entering DNA synthesis after viral infection by inhibition 5 of essential S-phase initiating activities such as CDK2, may disrupt the virus life cycle by preventing virus replication. This same principle may be used to protect normal cells of the body from toxicity of cycle-specific chemotherapeutic agents. Inhibition of CDK2 or CDK4 will 10 prevent progression into the cycle in normal cells and limit the toxicity of cytotoxics which act in S-phase, G2 or mitosis. Furthermore, CDK2/cyclin E activity has also been shown to regulate NF- κ B: Inhibition of CDK2 activity stimulates NF- κ B-dependent gene expression, an event 15 mediated through interactions with the p300 coactivator. NF- κ B regulates genes involved in inflammatory responses, (such as hematopoietic growth factors chemokines and leukocyte adhesion molecules) and may be involved in the suppression of apoptotic signals within the cell. Thus, 20 inhibition of CDK2 may suppress apoptosis induced by cytotoxic drugs via a mechanism which involves NF- κ B. Inhibition of CDK2 activity may also have utility in other cases where regulation of NF- κ B plays a role in etiology of disease. A further example may be taken from fungal 25 infections: Inhibition of the *Aspergillus* kinases Cdc2/CDC28 or Nim A may cause arrest or death in the fungi, improving the therapeutic outcome for patients with these infections.

The compounds of the invention are useful as 30 modulators of apoptosis. As such they are useful in the prevention of AIDS development in HIV-infected individuals, autoimmune diseases (including but not limited to systemic lupus, erythematosus, autoimmune mediated glomerulonephritis, rheumatoid arthritis and autoimmune

diabetes mellitus), myelodysplastic syndromes, aplastic anemia, ischemic injury associated with myocardial infarctions, stroke and reperfusion injury, vision related disorders including but not limited to glaucoma and macular 5 degeneration, arrhythmia, atherosclerosis, toxin-induced or alcohol related liver diseases, hematological diseases (including but not limited to chronic anemia and aplastic anemia), degenerative diseases of the musculoskeletal system (including but not limited to osteoporosis) aspirin-10 sensitive rhinosinusitis, cystic fibrosis, kidney diseases and cancer pain.

Definitions

The term "prevention" includes either 15 preventing the onset of disorders altogether or delaying the onset of a preclinically evident stage of disorders in individuals. This includes prophylactic treatment of those at risk of developing a disease, such as a cancer, for 20 example.

The phrase "therapeutically-effective" is intended to qualify the amount of each agent, which will achieve the goal of improvement in disorder severity and the frequency of incidence over treatment of each agent by itself, while 25 avoiding adverse side effects typically associated with alternative therapies. For example, effective neuroplastic therapeutic agents prolong the survivability of the patient, inhibit the rapidly-proliferating cell growth associated with the neoplasm, or effect a regression of the neoplasm. 30 Alternatively, effective therapeutic agents for the treatment of neurological disorders minimize the damage from injury, improve cognitive functions, and the like.

The term "H" denotes a single hydrogen atom. This radical may be attached, for example, to an oxygen atom to form a hydroxyl radical.

Where the term "alkyl" is used, either alone or within other terms such as "haloalkyl" and "alkylamino", it embraces linear or branched radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl and the like. Even more preferred are lower alkyl radicals having one to four carbon atoms. The term "alkylenyl" embraces bridging divalent alkyl radicals such as methylenyl and ethylenyl.

The term "alkenyl" embraces linear or branched radicals having at least one carbon-carbon double bond of two to about twenty carbon atoms or, preferably, two to about twelve carbon atoms. More preferred alkenyl radicals are "lower alkenyl" radicals having two to about four carbon atoms. Examples of alkenyl radicals include ethenyl, propenyl, allyl, propenyl, butenyl and 4-methylbutenyl. The terms "alkenyl" and "lower alkenyl", embrace radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations.

The term "alkynyl" denotes linear or branched radicals having two to about twenty carbon atoms or, preferably, two to about twelve carbon atoms. More preferred alkynyl radicals are "lower alkynyl" radicals having two to about ten carbon atoms. Most preferred are lower alkynyl radicals having two to about four carbon atoms. Examples of such radicals include propargyl, butynyl, and the like.

The term "halo" means halogens such as fluorine, chlorine, bromine or iodine atoms.

The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. "Lower haloalkyl" embraces radicals having 1-6 carbon atoms. Even more preferred are lower haloalkyl radicals having one to three carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. "Perfluoroalkyl" means alkyl radicals having all hydrogen atoms replaced with fluoro atoms. Examples include trifluoromethyl and pentafluoroethyl.

The term "hydroxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. More preferred hydroxyalkyl radicals are "lower hydroxyalkyl" radicals having one to six carbon atoms and one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and hydroxyhexyl. Even more preferred are lower hydroxyalkyl radicals having one to three carbon atoms.

The term "azidoalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more azido (N_3) radicals. More preferred azidoalkyl radicals are "lower azidoalkyl" radicals having one to six carbon atoms and one azido radical. Examples of such radicals include

azidomethyl. Even more preferred are lower azidoalkyl radicals having one to three carbon atoms.

The term "cyanoalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more cyano (CN) radicals. More preferred cyanoalkyl radicals are "lower cyanoalkyl" radicals having one to six carbon atoms and one cyano radical. Examples of such radicals include cyanomethyl. Even more preferred are lower cyanoalkyl radicals having one to three carbon atoms.

The term "phenyloxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more phenoxy radicals. More preferred phenyloxyalkyl radicals are "lower phenyloxyalkyl" radicals having one to six carbon atoms and one phenoxy radical. Examples of such radicals include phenoxyethyl.

The term "alkoxy" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and tert-butoxy. Even more preferred are lower alkoxy radicals having one to three carbon atoms. The "alkoxy" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkoxy" radicals. Even more preferred are lower haloalkoxy radicals having one to three carbon atoms. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, trifluoroethoxy, fluoroethoxy and fluoropropoxy.

The term "alkoxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more alkoxy

radicals. More preferred alkoxyalkyl radicals are "lower alkoxyalkyl" radicals having one to six carbon atoms and one alkoxy radical. Examples of such radicals include methoxymethyl.

5 The term "aminoalkoxyalkyl" embraces alkoxyalkyl radicals, as defined above, where any one carbon atom may be substituted with one amino radical. More preferred aminoalkoxyalkyl radicals are "lower aminoalkoxyalkyl" radicals having one to six carbon atoms. Examples of such 10 radicals include aminoethoxymethyl.

The term "alkylaminoalkoxy" embraces alkoxy radicals, as defined above, substituted with an alkylamino radical. More preferred alkylaminoalkoxy radicals are "lower alkylaminoalkoxy" radicals having alkoxy groups with one to 15 six carbon atoms and an alkylamino radical with one to six carbon atoms. Examples of such radicals include methylaminomethoxy.

The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one or two rings 20 wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl. More preferred aryl is phenyl. Said "aryl" group may have 1 to 3 substituents such as lower 25 alkyl, hydroxyl, halo, haloalkyl, nitro, cyano, alkoxy and lower alkylamino.

The term "heterocyclyl" embraces saturated, partially saturated and unsaturated heteroatom-containing ring-shaped radicals, where the heteroatoms may be selected from 30 nitrogen, sulfur and oxygen. It does not include rings containing -O-O-, -O-S- or -S-S- portions. Said "heterocyclyl" group may have 1 to 3 substituents such as BOC, hydroxyl, halo, haloalkyl, cyano, lower alkyl, lower aralkyl, oxo, lower alkoxy, amino and lower alkylamino.

Examples of saturated heterocyclic radicals include saturated 3 to 6-membered heteromonocyclic group containing 1 to 4 nitrogen atoms [e.g. pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. morpholinyl]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., thiazolidinyl].

Examples of partially saturated heterocyclyl radicals include dihydrothiophene, dihydropyran, dihydrofuran and dihydrothiazole.

Examples of unsaturated heterocyclic radicals, also termed "heteroaryl" radicals, include unsaturated 5 to 6 membered heteromonocyclyl group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl [e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl]; unsaturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, 2-furyl, 3-furyl, etc.; unsaturated 5 to 6-membered heteromonocyclic group containing a sulfur atom, for example, 2-thienyl, 3-thienyl, etc.; unsaturated 5- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl [e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl]; unsaturated 5 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl [e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl].

The term also embraces radicals where heterocyclic radicals are fused/condensed with aryl radicals: unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl,

indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl [e.g., tetrazolo [1,5-b]pyridazinyl]; unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 5 nitrogen atoms [e.g. benzoxazolyl, benzoxadiazolyl]; unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., benzothiazolyl, benzothiadiazolyl].

The term also includes bridged, spiro and oxo-10 containing heterocyclic rings, such as 1,4-dioxa-8-aza-spiro[4.5]decyl, phthalimidyl, 1,4-dioxa-8-aza-spiro[4.5]decyl, and (1-aza-bicyclo[2.2.2]oct-3-yl).

Preferred heterocyclic radicals include five to ten membered fused or unfused radicals. More preferred examples 15 of heteroaryl radicals include quinolyl, isoquinolyl, imidazolyl, pyridyl, thienyl, thiazolyl, oxazolyl, furyl, and pyrazinyl. Even more preferred heteroaryl radicals are 5- or 6-membered heteroaryl, containing one or two heteroatoms selected from sulfur nitrogen and oxygen, 20 selected from thienyl, furanyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyridyl, piperidinyl and pyrazinyl.

The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively 25 divalent radicals $-SO_2-$.

The terms "sulfamyl," "aminosulfonyl" and "sulfonamidyl," whether alone or used with terms such as "N-alkylaminosulfonyl", "N-arylaminosulfonyl", "N,N-dialkylaminosulfonyl" and "N-alkyl-N-arylaminosulfonyl", 30 denotes a sulfonyl radical substituted with an amine radical, forming a sulfonamide ($-SO_2NH_2$).

The term "alkylaminosulfonyl" includes "N-alkylaminosulfonyl" and "N,N-dialkylaminosulfonyl" where sulfamyl radicals are substituted, respectively, with one

alkyl radical, or two alkyl radicals. More preferred alkylaminosulfonyl radicals are "lower alkylaminosulfonyl" radicals having one to six carbon atoms. Even more preferred are lower alkylaminosulfonyl radicals having one to three 5 carbon atoms. Examples of such lower alkylaminosulfonyl radicals include N-methylaminosulfonyl, N-ethylaminosulfonyl and N-methyl-N-ethylaminosulfonyl.

The terms "N-arylaminosulfonyl" and "N-alkyl-N-arylaminosulfonyl" denote sulfamyl radicals substituted, 10 respectively, with one aryl radical, or one alkyl and one aryl radical. More preferred N-alkyl-N-arylaminosulfonyl radicals are "lower N-alkyl-N-arylsulfonyl" radicals having alkyl radicals of one to six carbon atoms. Even more preferred are lower N-alkyl-N-arylsulfonyl radicals having 15 one to three carbon atoms. Examples of such lower N-alkyl-N-aryl-aminosulfonyl radicals include N-methyl-N-phenylaminosulfonyl and N-ethyl-N-phenylaminosulfonyl. Examples of such N-aryl-aminosulfonyl radicals include N-phenylaminosulfonyl, which may be optionally substituted on 20 the phenyl ring.

The term "arylalkylaminosulfonyl" embraces aralkyl radicals as described above, attached to an aminosulfonyl radical. More preferred are lower arylalkylaminosulfonyl radicals having one to three carbon atoms.

25 The term "heterocyclylaminosulfonyl" embraces heterocyclyl radicals as described above, attached to an aminosulfonyl radical.

The term "heterocyclylsulfonylalkyl" embraces 30 heterocyclyl radicals as described above, attached to an alkyl radical through a sulfonyl linker. More preferred are "lower heterocyclylsulfonylalkyl" wherein the alkyl portion is one to six carbons long. Even more preferred, the alkyl portions are 1-3 carbons long.

The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes $-\text{CO}_2\text{H}$.

The term "carbonyl", whether used alone or with other terms, such as "aminocarbonyl", denotes $-(\text{C}=\text{O})-$.

5 The term "aminocarbonyl" when used by itself or with other terms such as "aminocarbonylalkyl", "N-alkylaminocarbonyl", "N-arylaminocarbonyl", "N,N-dialkylaminocarbonyl", "N-alkyl-N-arylaminocarbonyl", "N-alkyl-N-hydroxyaminocarbonyl" and "N-alkyl-N-10 hydroxyaminocarbonylalkyl", denotes an amide group of the formula $-\text{C}(=\text{O})\text{NH}_2$.

The term "alkoxycarbonyl" denotes an ester group wherein the carbonyl group is substituted with an alkoxy radical, as described above. The carbonyl portion is the 15 point of attachment. More preferred are "lower aloxycarbonyl" having lower alkoxy radicals as described above attached to a carbonyl radical.

The terms "N-alkylaminocarbonyl" and "N,N-dialkylaminocarbonyl" denote aminocarbonyl radicals which 20 have been substituted with one alkyl radical and with two alkyl radicals, respectively. More preferred are "lower alkylaminocarbonyl" having lower alkyl radicals as described above attached to an aminocarbonyl radical.

The term "alkylamino-alkylaminocarbonyl" denotes 25 alkylaminocarbonyl radicals which have been substituted with an alkylamino radical. More preferred are "lower alkylamino-alkylaminocarbonyl" having lower alkyl radicals, as described above.

The terms "N-arylaminocarbonyl" and "N-alkyl-N-30 arylaminocarbonyl" denote aminocarbonyl radicals substituted, respectively, with one aryl radical, or one alkyl and one aryl radical.

The term "heterocyclalkylaminocarbonyl" denotes aminocarbonyl radicals substituted with a heterocyclalkyl radical.

The term "heterocyclcarbonyl" denotes carbonyl 5 radicals substituted with a heterocycl radical.

The term "aminoalkyl" embraces alkyl radicals substituted with amino radicals.

The term "alkylaminothiocarbonyl" denotes thioamide compounds comprising thiocarbonyl radicals (-C(S)-) which 10 have been substituted with an alkylamino radicals. More preferred are "lower alkylaminothiocarbonyl" having lower alkyl radicals as described above.

The term "alkylaminoalkyl" embraces aminoalkyl radicals having the nitrogen atom substituted with an alkyl 15 radical. The term includes both mono- and di-substituted amines. Even more preferred are lower alkylaminoalkyl radicals having one to three carbon atoms.

The term "heterocyclalkyl" embraces heterocyclic-substituted alkyl radicals. More preferred heterocyclalkyl 20 radicals are "5- or 6-membered heteroarylalkyl" radicals having alkyl portions of one to six carbon atoms and a 5- or 6-membered heteroaryl radical. Even more preferred are lower heteroarylalkyl radicals having alkyl portions of one to three carbon atoms. Examples include such radicals as 25 pyridylmethyl and thienylmethyl.

The term "aralkyl" embraces aryl-substituted alkyl radicals. Preferable aralkyl radicals are "lower aralkyl" radicals having aryl radicals attached to alkyl radicals having one to six carbon atoms. Even more preferred are 30 lower aralkyl radicals phenyl attached to alkyl portions having one to three carbon atoms. Examples of such radicals include benzyl, diphenylmethyl and phenylethyl. The aryl in said aralkyl may be additionally substituted with halo, alkyl, alkoxy, haloalkyl and haloalkoxy.

The term "arylalkenyl" embraces aryl-substituted alkenyl radicals. Preferable arylalkenyl radicals are "lower arylalkenyl" radicals having aryl radicals attached to alkenyl radicals having two to six carbon atoms. Examples of 5 such radicals include phenylethenyl. The aryl in said arylalkenyl may be additionally substituted with halo, alkyl, alkoxy, haloalkyl and haloalkoxy.

The term "arylalkynyl" embraces aryl-substituted alkynyl radicals. Preferable arylalkynyl radicals are "lower 10 arylalkynyl" radicals having aryl radicals attached to alkynyl radicals having two to six carbon atoms. Examples of such radicals include phenylethynyl. The aryl in said aralkyl may be additionally substituted with halo, alkyl, alkoxy, haloalkyl and haloalkoxy. The terms benzyl and 15 phenylmethyl are interchangeable.

The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. Even more preferred are lower alkylthio radicals having one to three 20 carbon atoms. An example of "alkylthio" is methylthio, $(\text{CH}_3\text{S}-)$.

The term "haloalkylthio" embraces radicals containing a haloalkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. Even more preferred are lower 25 haloalkylthio radicals having one to three carbon atoms. An example of "haloalkylthio" is trifluoromethylthio.

The term "alkylsulfinyl" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent $-\text{S}(=\text{O})-$ atom. More preferred 30 are lower alkylsulfinyl radicals having one to three carbon atoms.

The term "arylsulfinyl" embraces radicals containing an aryl radical, attached to a divalent $-\text{S}(=\text{O})-$ atom. Even

more preferred are optionally substituted phenylsulfinyl radicals.

The term "haloalkylsulfinyl" embraces radicals containing a haloalkyl radical, of one to ten carbon atoms, 5 attached to a divalent $-S(=O)-$ atom. Even more preferred are lower haloalkylsulfinyl radicals having one to three carbon atoms.

The term "alkylamino" denotes amino groups which have been substituted with one alkyl radical and with two alkyl 10 radicals, including terms "N-alkylamino" and "N,N-dialkylamino". More preferred alkylamino radicals are "lower alkylamino" radicals having one or two alkyl radicals of one to six carbon atoms, attached to a nitrogen atom. Even more preferred are lower alkylamino radicals having one to three 15 carbon atoms. Suitable "alkylamino" may be mono or dialkylamino such as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino or the like.

The term "hydroxyalkylamino" denotes amino groups which have been substituted with a hydroxyalkyl radical, as 20 defined above.

The term "heterocyclalkylamino" denotes alkylamino groups which have been substituted with a heterocyclyl radical, as defined above.

The term "arylamino" denotes amino groups which have been substituted with one or two aryl radicals, such as N-phenylamino. The "arylamino" radicals may be further substituted on the aryl ring portion of the radical.

The term "heteroarylamino" denotes amino groups which have been substituted with one or two heteroaryl radicals, 30 such as N-thienylamino. The "heteroarylamino" radicals may be further substituted on the heteroaryl ring portion of the radical.

The term "aralkylamino" denotes amino groups which have been substituted with one or two aralkyl radicals. More

preferred are phenyl-C₁-C₃-alkylamino radicals, such as N-benzylamino. The "aralkylamino" radicals may be further substituted on the aryl ring portion of the radical.

5 The terms "N-alkyl-N-arylamino" and "N-aralkyl-N-alkylamino" denote amino groups which have been substituted with one aralkyl and one alkyl radical, or one aryl and one alkyl radical, respectively, to an amino group.

10 The term "arylthio" embraces aryl radicals of six to ten carbon atoms, attached to a divalent sulfur atom. An example of "arylthio" is phenylthio.

The term "aralkylthio" embraces aralkyl radicals as described above, attached to a divalent sulfur atom. More preferred are phenyl-C₁-C₃-alkylthio radicals. An example of "aralkylthio" is benzylthio.

15 The term "aryloxy" embraces optionally substituted aryl radicals, as defined above, attached to an oxygen atom. Examples of such radicals include phenoxy.

20 The term "heterocyclyloxy" embraces optionally substituted heterocyclyl radicals, as defined above, attached to an oxygen atom. Examples of such radicals include pyrrolidinyloxy, piperidinyloxy, and pyridyloxy.

25 The term "aralkoxy" embraces oxy-containing aralkyl radicals attached through an oxygen atom to other radicals. More preferred aralkoxy radicals are "lower aralkoxy" radicals having optionally substituted phenyl radicals attached to lower alkoxy radical as described above.

30 The term "heterocyclalkoxy" embraces oxy-containing heterocyclalkyl radicals attached through an oxygen atom to other radicals. More preferred heterocyclyloxy radicals are "lower heterocyclyloxy" radicals having optionally substituted 5-6 membered heterocyclyl radicals attached to lower alkoxy radical as described above.

The term "cycloalkyl" includes saturated carbocyclic groups. Preferred cycloalkyl groups include C₃-C₆ rings.

More preferred compounds include, for example, cyclopropyl, cyclopentyl and cyclohexyl.

The term "cycloalkenyl" includes carbocyclic groups having one or more carbon-carbon double bonds.

5 "Cycloalkenyl" and "cycloalkyldienyl" compounds are included. Preferred cycloalkenyl groups include C₃-C₆ rings. More preferred compounds include, for example, cyclopentenyl, cyclopentadienyl, cyclohexenyl and cycloheptadienyl.

10 The term "comprising" is meant to be open ended, including the indicated component but not excluding other elements.

The present invention preferably includes compounds that selectively inhibit GSK, CDK2 and/or CDK5.

15 The present invention also comprises the use of a compound of the invention, or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment either acutely or chronically of a cell proliferation or apoptosis mediated disease state, including
20 those described previously. The compounds of the present invention are also useful in the manufacture of an anti-cancer medicament. The compounds of the present invention are also useful in the manufacture of a medicament to attenuate or prevent disorders through inhibition of CDKs
25 and other kinases. The compounds of the present invention are also useful in the manufacture of a medicament to treat neurological disorders.

The present invention comprises a pharmaceutical composition comprising a therapeutically-effective amount of
30 a compound of Formulas I-VI in association with a least one pharmaceutically-acceptable carrier, adjuvant or diluent.

The present invention also comprises a method of treating cell proliferative disorders, apoptosis mediated disorders, cancer, CDK mediated disorder or neurological

disorders, in a subject, the method comprising treating the subject having or susceptible to such disorder with a therapeutically-effective amount of a compound of Formulas I-VI.

5

COMBINATIONS

While the compounds of the invention can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more compounds 10 of the invention or other agents. When administered as a combination, the therapeutic agents can be formulated as separate compositions that are administered at the same time or sequentially at different times, or the therapeutic agents can be given as a single composition.

15 The phrase "co-therapy" (or "combination-therapy"), in defining use of a compound of the present invention and another pharmaceutical agent, is intended to embrace administration of each agent in a sequential manner in a regimen that will provide beneficial effects of the drug 20 combination, and is intended as well to embrace co-administration of these agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of these active agents or in multiple, separate capsules for each agent.

25 Specifically, the administration of compounds of the present invention may be in conjunction with additional therapies known to those skilled in the art in the treatment of neoplasia, such as with radiation therapy or with cytostatic or cytotoxic agents; or in the treatment of 30 neurological disorders, such as with thrombolytic and anticoagulant agents, anti-inflammatory agents, NMDA inhibitors, antiparkinsonian agents, and inhibitors of lipid peroxidation.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the accepted dosage ranges. Compounds of Formula I-VI may also be administered sequentially with known agents when a 5 combination formulation is inappropriate. The invention is not limited in the sequence of administration; compounds of the invention may be administered either prior to, at the same time with or after administration of the other agent.

Currently, standard treatment of primary tumors 10 consists of surgical excision followed by either radiation or IV administered chemotherapy. The typical chemotherapy regime consists of either DNA alkylating agents, DNA intercalating agents or microtubule poisons. The chemotherapy doses used are just below the maximal tolerated 15 dose and therefore dose limiting toxicities typically include, nausea, vomiting, diarrhea, hair loss, neutropenia and the like. Experiments performed in *in vivo* animal models and in *in vitro* cell based assays have demonstrated that combining chemotherapeutic agents with cell cycle 20 inhibitors, such as CDK inhibitors, typically results in either decreased rate of tumor growth or, in some cases, tumor regression. Combining chemotherapy with a CDK inhibitor typically results in an increased therapeutic index and lower levels of both agents are required. This 25 ultimately results in a decrease in toxicity and an increase in efficacy.

Schwartz et al, Clin. Can. Res., 3,1467-1472 (1997) have demonstrated that combining the CDK inhibitor flavopiridol with mitomycin-C (DNA alkylating agent) 30 resulted in an increased rate of apoptosis in gastric and breast cancer cells. Bible et al (Bible et al., Cancer Res., 57, 3375-3380 (1997) have also demonstrated therapeutic synergy exists between flavopiridol and paclitaxel, cytarabine, topotecan, doxorubicin, and etoposide (all

standard chemotherapeutic agents) when tested in cell based assays using human non-small cell lung cancer cells. Preclinical models (cell culture) suggest that a cell cycle inhibitor potentiates the effect of a cytotoxic agent when 5 administered after the chemotherapeutic agent. The chemotherapeutic agent will induce specific DNA/mitotic damage checkpoints in normal cells which in combination with a CDK inhibitor will cause a cell cycle arrest or cytostatic effect. In contrast, tumor cells will be driven into 10 apoptosis or cell death when a chemotherapeutic agent and a CDK inhibitor are combined due to tumor cells attempting to activate defective DNA damage and cell cycle checkpoints. In addition, scheduling of a CDK inhibitor for clinical trials should include a rest period to allow the patients normal 15 cells to recover and reduce the potential for cytotoxic side effects.

There are large numbers of antineoplastic agents available in commercial use, in clinical evaluation and in pre-clinical development, which would be selected for 20 treatment of neoplasia by combination drug chemotherapy. Such antineoplastic agents fall into several major categories, namely, antibiotic-type agents, alkylating agents, antimetabolite agents, hormonal agents, immunological agents, interferon-type agents and a category 25 of miscellaneous agents.

A first family of antineoplastic agents which may be used in combination with compounds of the present invention consists of antimetabolite-type/thymidilate synthase inhibitor antineoplastic agents. Suitable antimetabolite 30 antineoplastic agents may be selected from but not limited to the group consisting of 5-FU-fibrinogen, acanthifolic acid, aminothiadiazole, brequinar sodium, carmofur, Ciba-Geigy CGP-30694, cyclopentyl cytosine, cytarabine phosphate stearate, cytarabine conjugates, Lilly DATHF, Merrel Dow

DDFC, dezaguanine, dideoxycytidine, dideoxyguanosine, didox, Yoshitomi DMDC, doxifluridine, Wellcome EHNA, Merck & Co. EX-015, fazarabine, floxuridine, fludarabine phosphate, 5-fluorouracil, N-(2'-furanidyl)-5-fluorouracil, Daiichi
5 Seiyaku FO-152, isopropyl pyrrolizine, Lilly LY-188011, Lilly LY-264618, methobenzaprim, methotrexate, Wellcome MZPES, norspermidine, NCI NSC-127716, NCI NSC-264880, NCI NSC-39661, NCI NSC-612567, Warner-Lambert PALA, pentostatin, piritrexim, plicamycin, Asahi Chemical PL-AC, Takeda TAC-
10 788, thioguanine, tiazofurin, Erbamont TIF, trimetrexate, tyrosine protein kinase inhibitors, Taiho UFT and uricytin.

A second family of antineoplastic agents which may be used in combination with compounds of the present invention consists of alkylating-type antineoplastic agents. Suitable
15 alkylating-type antineoplastic agents may be selected from but not limited to the group consisting of Shionogi 254-S, aldo-phosphamide analogues, altretamine, anaxirone, Boehringer Mannheim BBR-2207, bestrabucil, budotitane, Wakunaga CA-102, carboplatin, carmustine, Chinoi-139,
20 Chinoi-153, chlorambucil, cisplatin, cyclophosphamide, American Cyanamid CL-286558, Sanofi CY-233, cyplatate, Degussa D-19-384, Sumimoto DACHP(Myr)2, diphenylspiromustine, diplatinum cytostatic, Erba distamycin derivatives, Chugai DWA-2114R, ITI E09, elmustine, Erbamont
25 FCE-24517, estramustine phosphate sodium, fotemustine, Unimed G-6-M, Chinoi GYKI-17230, hepsul-fam, ifosfamide, iproplatin, lomustine, mafosfamide, mitolactol, Nippon Kayaku NK-121, NCI NSC-264395, NCI NSC-342215, oxaliplatin, Upjohn PCNU, prednimustine, Proter PTT-119, ranimustine,
30 semustine, SmithKline SK&F-101772, Yakult Honsha SN-22, spiromus-tine, Tanabe Seiyaku TA-077, tauromustine, temozolomide, teroxirone, tetraplatin and trimelamol.

A third family of antineoplastic agents which may be used in combination with compounds of the present invention

consists of antibiotic-type antineoplastic agents. Suitable antibiotic-type antineoplastic agents may be selected from but not limited to the group consisting of Taiho 4181-A, aclarubicin, actinomycin D, actinoplanone, Erbamont ADR-456, 5 aeroplysinin derivative, Ajinomoto AN-201-II, Ajinomoto AN-3, Nippon Soda anisomycins, anthracycline, azino-mycin-A, bisucaberin, Bristol-Myers BL-6859, Bristol-Myers BMY-25067, Bristol-Myers BMY-25551, Bristol-Myers BMY-26605, Bristol-Myers BMY-27557, Bristol-Myers BMY-28438, bleomycin sulfate, 10 bryostatin-1, Taiho C-1027, calichemycin, chromoximycin, dactinomycin, daunorubicin, Kyowa Hakko DC-102, Kyowa Hakko DC-79, Kyowa Hakko DC-88A, Kyowa Hakko DC89-A1, Kyowa Hakko DC92-B, ditrisarubicin B, Shionogi DOB-41, doxorubicin, doxorubicin-fibrinogen, elسامین-A, epirubicin, erbstatin, 15 esorubicin, esperamicin-A1, esperamicin-Alb, Erbamont FCE-21954, Fujisawa FK-973, fostriecin, Fujisawa FR-900482, glidobactin, gregatin-A, grincamycin, herbimycin, idarubicin, illudins, kazusamycin, kesarirhodins, Kyowa Hakko KM-5539, Kirin Brewery KRN-8602, Kyowa Hakko KT-5432, 20 Kyowa Hakko KT-5594, Kyowa Hakko KT-6149, American Cyanamid LL-D49194, Meiji Seika ME 2303, menogaril, mitomycin, mitoxantrone, SmithKline M-TAG, neoenactin, Nippon Kayaku NK-313, Nippon Kayaku NKT-01, SRI International NSC-357704, oxalysine, oxaunomycin, peplomycin, pilatin, pirarubicin, 25 porothramycin, pyrindanycin A, Tobishi RA-I, rapamycin, rhizoxin, rodorubicin, sibanomicin, siwenmycin, Sumitomo SM-5887, Snow Brand SN-706, Snow Brand SN-07, sorangicin-A, sparsomycin, SS Pharmaceutical SS-21020, SS Pharmaceutical SS-7313B, SS Pharmaceutical SS-9816B, steffimycin B, Taiho 30 4181-2, talisomycin, Takeda TAN-868A, terpentine, thrazine, tricrozarin A, Upjohn U-73975, Kyowa Hakko UCN-10028A, Fujisawa WF-3405, Yoshitomi Y-25024 and zorubicin.

A fourth family of antineoplastic agents which may be used in combination with compounds of the present invention

consists of a miscellaneous family of antineoplastic agents, including tubulin interacting agents, topoisomerase II inhibitors, topoisomerase I inhibitors and hormonal agents, selected from but not limited to the group consisting of α -5 carotene, α -difluoromethyl-arginine, acitretin, Biotec AD-5, Kyorin AHC-52, alstonine, amonafide, amphethinile, amsacrine, Angiostat, ankinomycin, anti-neoplaston A10, antineoplaston A2, antineoplaston A3, antineoplaston A5, antineoplaston AS2-1, Henkel APD, aphidicolin glycinate, 10 asparaginase, Avarol, baccharin, batracylin, benfluron, benzotript, Ipsen-Beaufour BIM-23015, bisantrene, Bristol-Myers BMY-40481, Vestar boron-10, bromofosfamide, Wellcome BW-502, Wellcome BW-773, caracemide, carmethizole hydrochloride, Ajinomoto CDAF, chlorsulfaquinoxalone, Chemes 15 CHX-2053, Chemex CHX-100, Warner-Lambert CI-921, Warner-Lambert CI-937, Warner-Lambert CI-941, Warner-Lambert CI-958, clanfenur, claviridenone, ICN compound 1259, ICN compound 4711, Contracan, Yakult Honsha CPT-11, crisnatol, curaderm, cytochalasin B, cytarabine, cytosine, Merz D-609, 20 DABIS maleate, dacarbazine, datelliptinium, didemnin-B, dihaematoporphyrin ether, dihydrolenperone, dinaline, distamycin, Toyo Pharmar DM-341, Toyo Pharmar DM-75, Daiichi Seiyaku DN-9693, docetaxel elliprabin, elliptinium acetate, Tsumura EPMTC, the epothilones, ergotamine, etoposide, 25 etretinate, fenretinide, Fujisawa FR-57704, gallium nitrate, genkwadaphnin, Chugai GLA-43, Glaxo GR-63178, grifolan NMF-5N, hexadecylphosphocholine, Green Cross HO-221, homoharringtonine, hydroxyurea, BTG ICRF-187, ilmofosine, isoglutamine, isotretinoin, Otsuka JI-36, Ramot K-477, 30 Otsuak K-76COONa, Kureha Chemical K-AM, MECT Corp KI-8110, American Cyanamid L-623, leukoregulin, lonidamine, Lundbeck LU-23-112, Lilly LY-186641, NCI (US) MAP, marycin, Merrel Dow MDL-27048, Medco MEDR-340, merbarone, merocyanline derivatives, methylanilinoacridine, Molecular Genetics MGI-

136, minactivin, mitonafide, mitoquidone molidamol,
motretinide, Zenyaku Kogyo MST-16, N-(retinoyl)amino acids,
Nisshin Flour Milling N-021, N-acylated-dehydroalanines,
nafazatrom, Taisho NCU-190, nocodazole derivative,
5 Normosang, NCI NSC-145813, NCI NSC-361456, NCI NSC-604782,
NCI NSC-95580, ocreotide, Ono ONO-112, oquizanocine, Akzo
Org-10172, paclitaxel, pancratistatin, pazelliptine, Warner-
Lambert PD-111707, Warner-Lambert PD-115934, Warner-Lambert
PD-131141, Pierre Fabre PE-1001, ICRT peptide D,
10 piroxantrone, polyhaemtoporphyrin, polypreic acid, Efamol
porphyrin, probimane, procarbazine, proglumide, Invitron
protease nexin I, Tobishi RA-700, razoxane, Sapporo
Breweries RBS, restrictin-P, retelliptine, retinoic acid,
Rhone-Poulenc RP-49532, Rhone-Poulenc RP-56976, SmithKline
15 SK&F-104864, Sumitomo SM-108, Kuraray SMANCS, SeaPharm SP-
10094, spatol, spirocyclopropane derivatives,
spirogermanium, Unimed, SS Pharmaceutical SS-554,
stryptoldinone, Stypoldione, Suntory SUN 0237, Suntory SUN
2071, superoxide dismutase, Toyama T-506, Toyama T-680,
20 taxol, Teijin TEI-0303, teniposide, thaliblastine, Eastman
Kodak TJB-29, tocotrienol, topotecan, Topostin, Teijin TT-
82, Kyowa Hakko UCN-01, Kyowa Hakko UCN-1028, ukrain,
Eastman Kodak USB-006, vinblastine sulfate, vincristine,
vindesine, vinestramide, vinorelbine, vintripotol,
25 vinzolidine, withanolides and Yamanouchi YM-534.

Alternatively, the present compounds may also be used
in co-therapies with other anti-neoplastic agents, such as
acemannan, aclarubicin, aldesleukin, alemtuzumab,
alitretinoin, altretamine, amifostine, aminolevulinic acid,
30 amrubicin, amsacrine, anagrelide, anastrozole, ANCER,
ancestim, ARGLABIN, arsenic trioxide, BAM 002 (Novelos),
bexarotene, bicalutamide, broxuridine, capecitabine,
celecoxib, celmoleukin, cetrorelix, cladribine,
clotrimazole, cytarabine ocfosfate, DA 3030 (Dong-A),

A-706B
- 70 -

daclizumab, denileukin diftitox, deslorelin, dexamoxane,
dilazep, docetaxel, docosanol, doxercalciferol,
doxifluridine, doxorubicin, bromocriptine, carmustine,
cytarabine, fluorouracil, HIT diclofenac, interferon alfa,
daunorubicin, doxorubicin, tretinoin, edelfosine,
edrecolomab, eflornithine, emitefur, epirubicin, epoetin
beta, etoposide phosphate, exemestane, exisulind,
fadrozole, filgrastim, finasteride, fludarabine phosphate,
formestane, fotemustine, gallium nitrate, gemcitabine,
gemtuzumab zogamicin, gimeracil/oteracil/tegafur
combination, glycopine, goserelin, heptaplatin, human
chorionic gonadotropin, idarubicin, human fetal alpha fetoprotein,
ibandronic acid, idarubicin, imiquimod, interferon alfa,
interferon alfa-2a, interferon alfa-2b, interferon alfa-2, interferon
alfa-n3, interferon alfacon-1, interferon alfa-1a, interferon
interferon beta, interferon beta-1a, interferon gamma-1a, interferon
gamma-1b, interferon gamma, natural interferon alfa-N1, interferon
interleukin-1 beta, iobenguane, irinotecan,
irsgladine, lanreotide, LC 9018 (Yakult), leflunomide,
lenograstim, lentinan sulfate, letrozole, leukocyte alpha
interferon, leuprorelin, lonidamine, lovastatin, masoprocol,
liarozole, lobaplatin, levamisole + fluorouracil,
melarsoprol, metoclopramide, mifepristone, miltefosine,
mitolactol, mitoxantrone, molgramostim, nafarelin, naloxone
+ pentazocine, nartograstim, nedaplatin, nilutamide,
noscapine, novel erythropoiesis stimulating protein, NSC
631570 octreotide, oprelvekin, osaterone, oxaliplatin,
paclitaxel, pamidronic acid, pegaspargase, peginterferon
alfa-2b, pentosan polysulfate sodium, pentostatin,
picibanil, pirarubicin, rabbit antithymocyte polyclonal
antibody, polyethylene glycol interferon alfa-2a, porfimer
sodium, raloxifene, raltitrexed, rasburicase, rhenium Re

186 etidronate, RII retinamide, rituximab, romurtide,
samarium (153 Sm) lexitronam, sargramostim, sizofiran,
sobuzoxane, sonermin, strontium-89 chloride, suramin,
tasonermin, tazarotene, tegafur, temoporfin, temozolomide,
5 teniposide, tetrachlorodecaoxide, thalidomide, thymalfasin,
thyrotropin alfa, topotecan, toremifene, tositumomab-iodine
131, trastuzumab, treosulfan, tretinoin, trilostane,
trimetrexate, triptorelin, tumor necrosis factor alpha,
natural, ubenimex, bladder cancer vaccine, Maruyama
10 vaccine, melanoma lysate vaccine, valrubicin, verteporfin,
vinorelbine, VIRULIZIN, zinostatin stimalamer, or
zoledronic acid; abarelix; AE 941 (Aeterna), ambamustine,
antisense oligonucleotide, bcl-2 (Genta), APC 8015
(Dendreon), cetuximab, decitabine, dexamino glutethimide,
15 diaziquone, EL 532 (Elan), EM 800 (Endorecherche),
eniluracil, etanidazole, fenretinide, filgrastim SD01
(Amgen), fulvestrant, galocitabine, gastrin 17 immunogen,
HLA-B7 gene therapy (Vical), granulocyte macrophage colony
stimulating factor, histamine dihydrochloride, ibritumomab
20 tiuxetan, ilomastat, IM 862 (Cytran), interleukin-2,
iproxifene, LDI 200 (Milkhaus), leridistim, lintuzumab, CA
125 MAb (Biomира), cancer MAb (Japan Pharmaceutical
Development), HER-2 and Fc MAb (Medarex), idiotypic 105AD7
MAb (CRC Technology), idiotypic CEA MAb (Trilex), LYM-1-
25 iodine 131 MAb (Technicclone), polymorphic epithelial mucin-
yttrium 90 MAb (Antisoma), marimastat, menogaril,
mitumomab, motexafin gadolinium, MX 6 (Galderma),
nelarabine, nolatrexed, P 30 protein, pegvisomant,
pemetrexed, porfiromycin, prinomastat, RL 0903 (Shire),
30 rubitecan, satraplatin, sodium phenylacetate, sparfosic
acid, SRL 172 (SR Pharma), SU 5416 (SUGEN), TA 077
(Tanabe), tetrathiomolybdate, thaliblastine,
thrombopoietin, tin ethyl etiopurpurin, tirapazamine,
cancer vaccine (Biomира), melanoma vaccine (New York

University), melanoma vaccine (Sloan Kettering Institute), melanoma oncolysate vaccine (New York Medical College), viral melanoma cell lysates vaccine (Royal Newcastle Hospital), or valsphospor.

5 Alternatively, the present compounds may also be used in co-therapies with other anti-neoplastic agents, such as other kinase inhibitors including KDR inhibitors, p38 inhibitors, TNF inhibitors, metallomatrix proteases inhibitors (MMP), COX-2 inhibitors, NSAID's, SOD mimics or
10 $\alpha_v\beta_3$ inhibitors.

15 Alternatively, the present compounds may also be used in co-therapies with other treatments for neurological treatments such as thrombolytic and anticoagulant agents including tPA, urokinase and inhibitors of platelet aggregation, p38 inhibitors, IL1ra, NMDA inhibitors, antiparkinsonian agents including carbidopa and levodopa, and inhibitors of lipid peroxidation, for example.

The present invention comprises a process for the preparation of a compound of Formula I-VI.

20 Compounds of the present invention can possess, in general, one or more asymmetric carbon atoms and are thus capable of existing in the form of optical isomers as well as in the form of racemic or non-racemic mixtures thereof. The optical isomers can be obtained by resolution of the
25 racemic mixtures according to conventional processes, e.g., by formation of diastereoisomeric salts, by treatment with an optically active acid or base. Examples of appropriate acids are tartaric, diacetyl tartaric, dibenzoyl tartaric, ditoluoyl tartaric, and camphorsulfonic acid and then
30 separation of the mixture of diastereoisomers by crystallization followed by liberation of the optically active bases from these salts. A different process for separation of optical isomers involves the use of a chiral chromatography column optimally chosen to maximize the

separation of the enantiomers. Still another available method involves synthesis of covalent diastereoisomeric molecules by reacting compounds of the invention with an optically pure acid in an activated form or an optically pure isocyanate. The synthesized diastereoisomers can be separated by conventional means such as chromatography, distillation, crystallization or sublimation, and then hydrolyzed to deliver the enantiomerically pure compound. The optically active compounds of the invention can likewise be obtained by using optically active starting materials. These isomers may be in the form of a free acid, a free base, an ester or a salt.

Compounds of the present invention can possess, in general, tautomeric forms, which are included in the family of compounds in Formula I-VI.

Also included in the family of compounds of Formula I-VI are the pharmaceutically-acceptable salts thereof. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts of compounds of Formula I-VI may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, arylaliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, example of which are formic, acetic, adipic, butyric, propionic, succinic, glycolic, gluconic, lactic, maleic, fumaric, tartaric, citric, ascorbic, glucuronic, benzoic, anthranilic, pyruvic, aspartic, glutamic, 4-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), mesylic,

methanesulfonic, ethanesulfonic, benzenesulfonic,
pantothenic, 2-hydroxyethanesulfonic, toluenesulfonic,
sulfanilic, cyclohexylaminosulfonic, camphoric,
camphorsulfonic, digluconic, cyclopentanepropionic,
5 dodecylsulfonic, glucoheptanoic, glycerophosphonic,
heptanoic, hexanoic, 2-hydroxy-ethanesulfonic, nicotinic, 2-
naphthalenesulfonic, oxalic, palmoic, pectinic, persulfuric,
2-phenylpropionic, picric, pivalic propionic, succinic,
tartaric, thiocyanic, mesylic, undecanoic, stearic, algenic,
10 β -hydroxybutyric, salicylic, galactaric and galacturonic
acid. Suitable pharmaceutically-acceptable base addition
salts of compounds of Formula I-VI include metallic salts,
such as salts made from aluminum, calcium, lithium,
magnesium, potassium, sodium and zinc, or salts made from
15 organic bases including primary, secondary and tertiary
amines, substituted amines including cyclic amines, such as
caffeine, arginine, diethylamine, N-ethyl piperidine,
aistidine, glucamine, isopropylamine, lysine, morpholine, N-
ethyl morpholine, piperazine, piperidine, triethylamine,
20 trimethylamine. All of these salts may be prepared by
conventional means from the corresponding compound of the
invention by reacting, for example, the appropriate acid or
base with the compound of Formula I-VI.

Also, the basic nitrogen-containing groups can be
25 quaternized with such agents as lower alkyl halides, such
as methyl, ethyl, propyl, and butyl chloride, bromides and
iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl,
and diamyl sulfates, long chain halides such as decyl,
lauryl, myristyl and stearyl chlorides, bromides and
30 iodides, aralkyl halides like benzyl and phenethyl
bromides, and others. Water or oil-soluble or dispersible
products are thereby obtained.

Examples of acids that may be employed to from
pharmaceutically acceptable acid addition salts include such

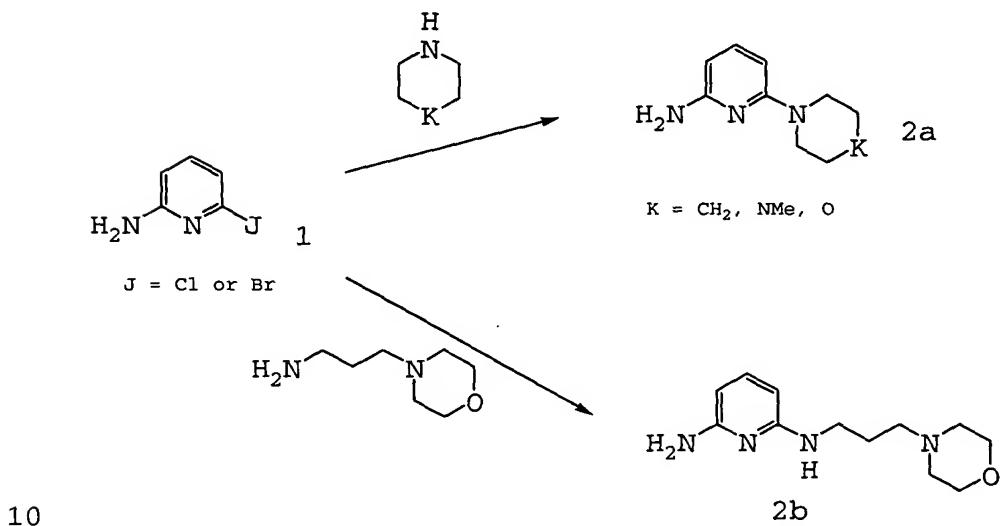
inorganic acids as HCl , H_2SO_4 and H_3PO_4 and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid. Other examples include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium or 5 magnesium or with organic bases.

Additional examples of such salts can be found in Berge et al., J. Pharm. Sci., 66, 1 (1977).

GENERAL SYNTHETIC PROCEDURES

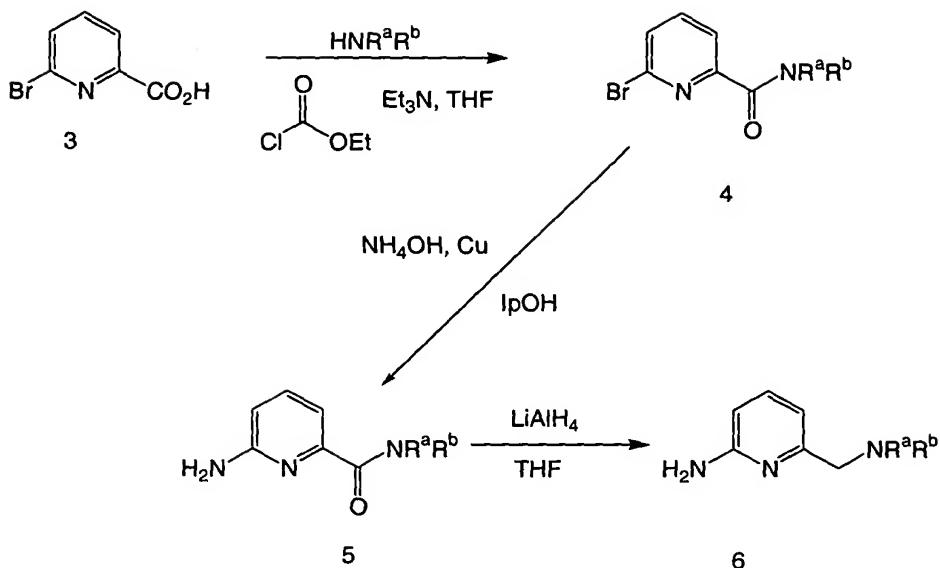
The compounds of the invention can be synthesized according to the following procedures of Schemes 1-24, 5 wherein the substituents are as defined for Formulas I-VI, above, except where further noted.

Scheme 1

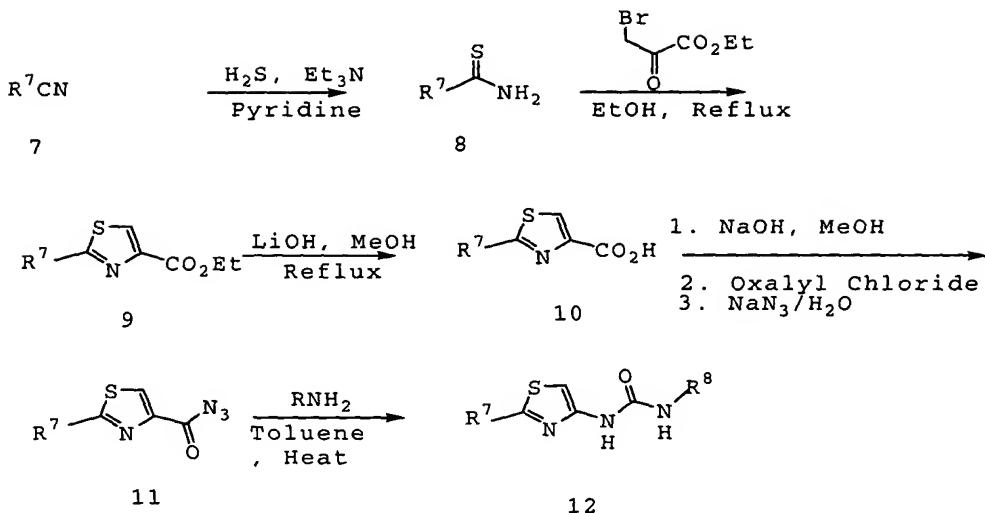


Substituted pyridines can be prepared according to the method set out in Scheme 1. A mixture of halo-aniline 1, substituted amine and phenol is reacted, preferably at a 15 temperature above RT and more preferably at temperature of about 150°C, to yield the heterocyclyl derivative 2a or substituted amine derivative 2b.

Sch m 2

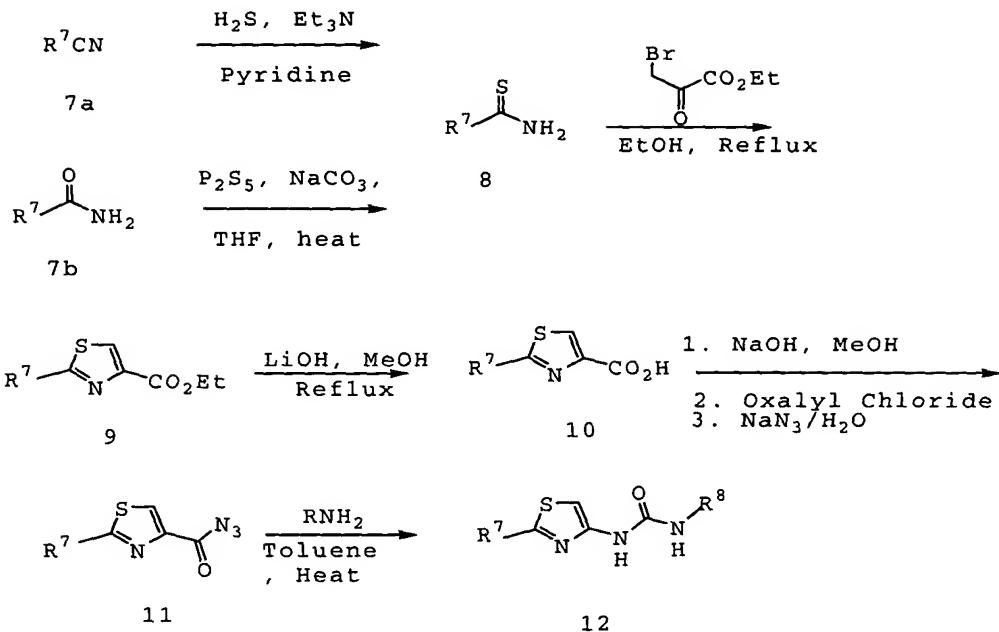


5 Substituted pyridines can be prepared according to the method set out in Scheme 2. A halopicolinic acid **3** is reacted with substituted amines (where R^a and R^b are H, alkyl, substituted alkyl, etc.) in the presence of chloroformate esters and base in a suitable solvent to form
10 the halopyridyl amide derivatives **4**. Preferably the reaction is at a temperature below RT, more preferably the reaction occurs at a temperature of about 0°C . The halopyridyl amide **4** is dehalogenated, such as with NH_4OH and Cu powder in an appropriate solvent, such as IpOH to form the aniline derivative **5**. Preferably the reaction occurs at a
15 temperature above RT, more preferably the reaction occurs at about 100°C . The aniline derivative **5** is reduced, such as with LiAlH_4 in Et_2O to form the aminoalkyl derivative **6**.

Scheme 3

5 Substituted 4-thiazolylurea compounds **12** are prepared
 from the corresponding nitriles **7** according to the method
 set out in Scheme 3. Substituted nitriles **7** are added to
 base at about RT and H_2S is bubbled through the solution, to
 yield the thione **8**. The thione **8** is combined with ethyl
 10 bromopyruvate and heated to form the thiazolyl carboxylate
 ester **9**. Aqueous $LiOH$ is heated with the ester **9** at a
 temperature above RT and preferably at reflux to give the
 thiazole carboxylic acid **10**. Treatment of the substituted
 thiazolyl carboxylic acid **10** with base in a suitable solvent
 15 at about RT yields a salt. At about $0^\circ C$, oxalyl chloride is
 added to a suspension of the salt in solvent followed by a
 catalytic amount of DMF. Afterwards, aqueous NaN_3 is added
 to yield the thiazolyl carbonyl azide **11**. The carbonyl
 azide **11** is added to substituted amines to form the
 20 thiazolyl urea compound **12**.

Scheme 4

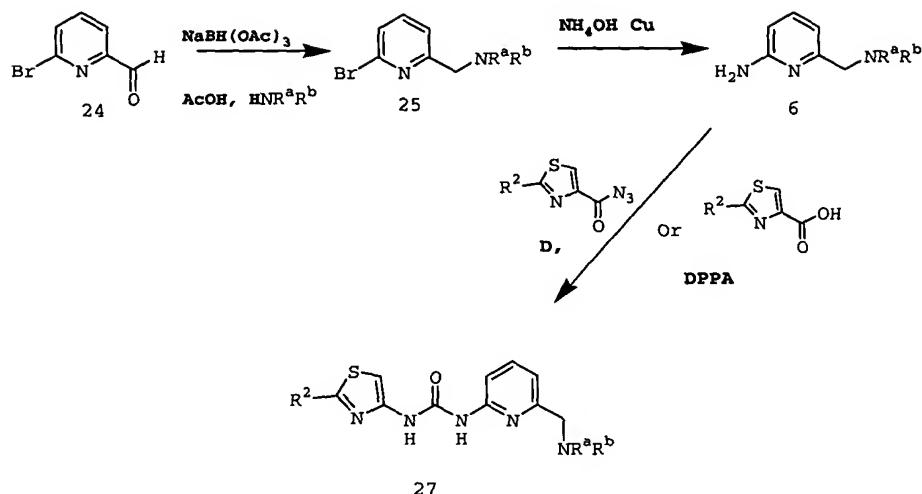


5 Substituted 4-thiazolylurea compounds **12** are prepared
 from either the corresponding nitriles **7a** or the
 corresponding amides **7b** according to the method set out in
 Scheme 3. Substituted nitriles **7a** are added to base at
 about RT and H_2S is bubbled through the solution, to yield
 10 the thione **8**. Alternatively, substituted amides **7b** are
 treated with P_2S_5 , NaCO_3 in THF and heated to give **8**. The
 thione **8** is combined with ethyl bromopyruvate and heated to
 form the thiazolyl carboxylate ester **9**. Aqueous LiOH is
 heated with the ester **9** at a temperature above RT and
 15 preferably at reflux to give the thiazole carboxylic acid
10. Treatment of the substituted thiazolyl carboxylic acid
10 with base in a suitable solvent at about RT yields a
 salt. At about 0°C , oxallyl chloride is added to a suspension
 of the salt in solvent followed by a catalytic amount of
 20 DMF. Afterwards, aqueous NaN_3 is added to yield the
 thiazolyl carbonyl azide **11**. The carbonyl azide **11** is added

to substituted amines to form the thiazolyl urea compound 12.

Scheme 5

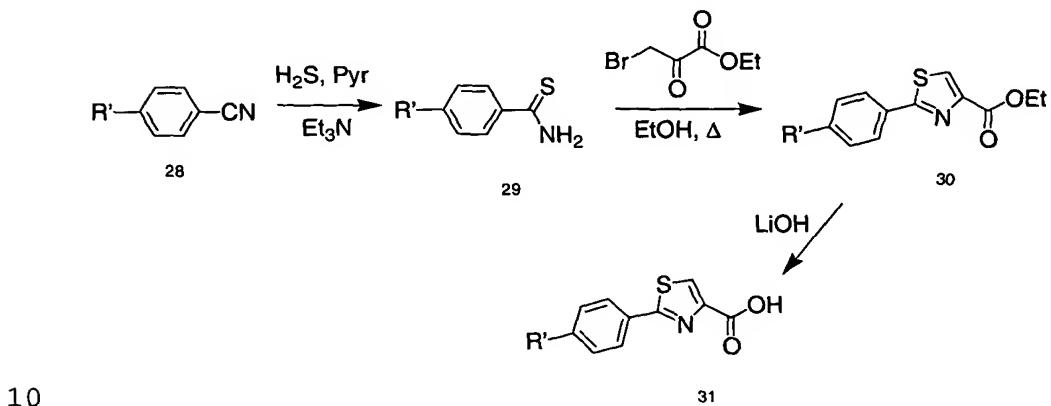
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Substituted 4-thiazolylurea compounds 27 are prepared from the corresponding pyridines 24 according to the method set out in Scheme 58. Reductive amination with an amine (including nitrogen-containing heterocycles) and 6-bromo-2-pyridinecarboxaldehyde 24, is achieved such as in a halocarbon solvent such as dichloromethane, in the presence of NaBH(OAc)_3 , and acid, such as AcOH, to give 2-aminomethyl-6-bromo-pyridine 25. The 2-aminomethyl-6-bromo-pyridine 25 is aminated, such as with NH_4OH in the presence of Cu powder, such as in the presence of an alcohol solvent, at a temperature above about 50°C and preferably at about 100°C, such as in a sealed tube to give the corresponding aniline 6. A substituted thiazolylcarbonylazide, such as in dry hydrocarbon solvent such as toluene is heated at a temperature above about 50°C and preferably above about 85°C and reacted with the aniline 6 to give the 4-thiazolylurea compounds 27.

Alternatively, the aniline **6** can be coupled with thiazolyl carboxylic acid, such as with DPPA in the presence of base, such as TEA, and molecular sieves in a solvent like THF. The reaction can be heated at a temperature above about 5 50°C and preferably at about reflux yielding the 4-thiazolylurea compounds **27**.

Scheme 9



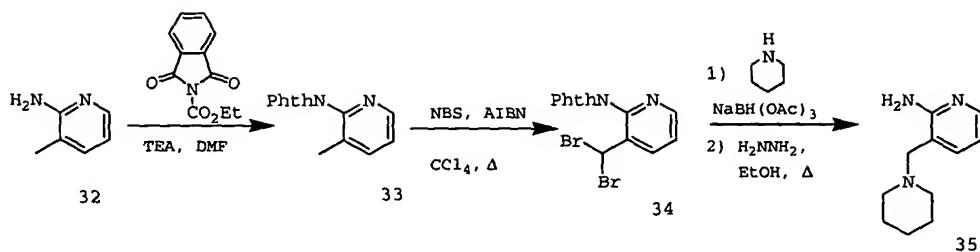
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Thiazolyl carboxylic acid **31** (especially appropriate where R' is a sulfonamide or amine) are prepared from the corresponding benzonitriles **28** as described in Scheme 9. 15 H₂S is added to the substituted 4-cyanobenzene **28** in the presence of base, such as Et₃N to afford the thiobenzamide **29**. The thiobenzamide **29** is reacted with ethyl bromopyruvate, such as in an alcohol solvent like EtOH, at a temperature greater than about 50°C, and preferably at about 20 75°C to give the thiazolyl ester **30**. The thiazolyl ester **30** is hydrolyzed, such as with LiOH monohydrate in an alcohol like aqueous MeOH, at a temperature greater than about 50°C, and preferably at about 75°C, to provide the acid **31**. The acid can be used similar to that described in Scheme 8.

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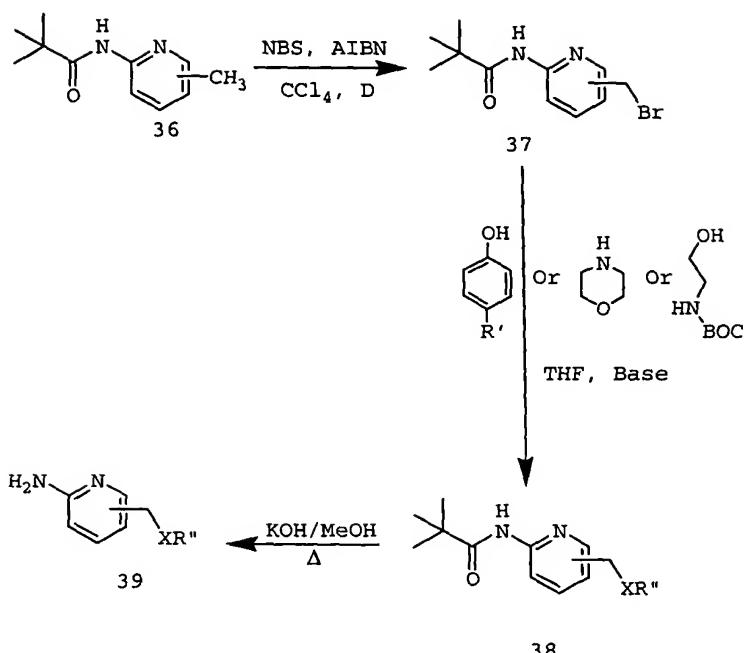
Scheme 10



5 Substituted anilines **35** are prepared from the corresponding methyl compounds **32** as described in Scheme 10. 2-Amino-3-picoline is protected such as with solid carboethoxyphthalimide and base like TEA to provide the phthalimide (Phth) protected aniline **32**. The protected 3-methylaniline is brominated, such as with NBS and AIBN at a temperature above 50°C and preferably at about reflux. Additional AIBN and NBS may be needed to push the reaction to completeness. The dibromomethyl aniline **34** is reacted with an amine, preferably a secondary amine such as 10 substituted or unsubstituted nitrogen containing heterocyclics like piperidines and piperazines, in the presence of acid like glacial AcOH and halocarbon solvent such as CH₂Cl₂. Treatment with NaBH(OAc)₃, provided the protected substituted methyl compound which is deprotected, 15 such as by treatment with hydrazine monohydrate at a temperature greater than about 50°C, and preferably at reflux to provide the substituted aniline **35**.

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Scheme 11



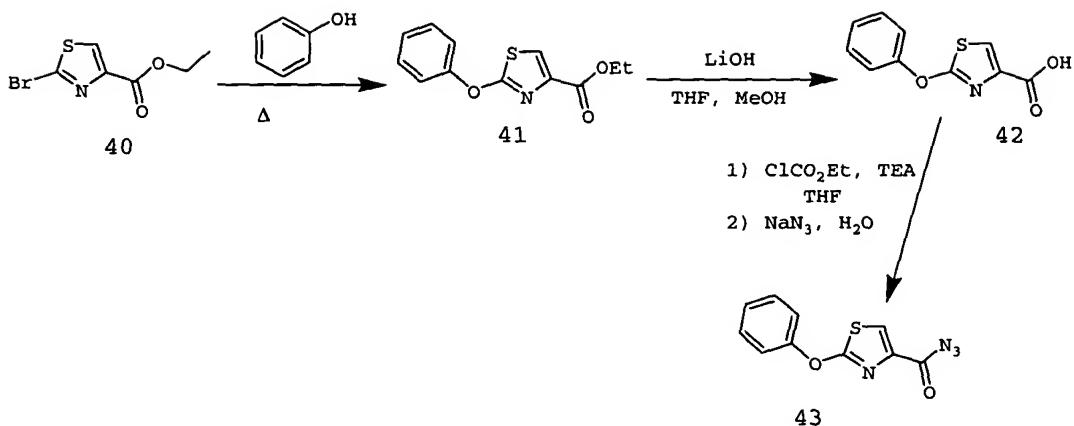
5

Substituted anilines 39 are prepared from the corresponding methyl compounds 36 as described in Scheme 11. N-Pivaloyl-2-amino-6-bromomethylpyridine 37 is prepared by the method of M.V. Papadopoulou, et al. (*J. Heterocyclic Chem.*, 1995, 32, 675-681). The protected bromomethyl compound is treated with an alcohol or amine in the presence of base, such as NaH to yield the corresponding ether or amino alkyl compounds 38 (where X is O or N). The protected ether or amino alkyl compounds 38 is treated with base, such as in methanolic KOH and warmed to a temperature greater than about RT, and preferably at about 55°C, to provide the substituted anilines 39.

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Scheme 12

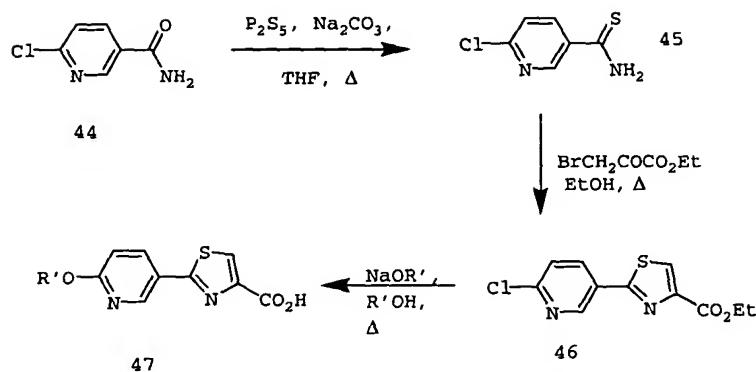


Thiazolylcarbonylazides **43** are prepared as described in Scheme 12. Bromothiazole is coupled with an aryl alcohol, such as phenol, at a temperature greater than about 100°C, and preferably at about 180°C, to provide the phenoxy compound **41**. The thiazolyl ester **41** is hydrolyzed, such as with LiOH monohydrate in an alcohol like aqueous MeOH, at a temperature greater than about 50°C, and preferably at about 75°C, to provide the acid **42**. Acid **42** is added to ethyl chloroformate and NaN₃, in the presence of base such as TEA, to provide the azide **43**, which can be used as described in Scheme 8.

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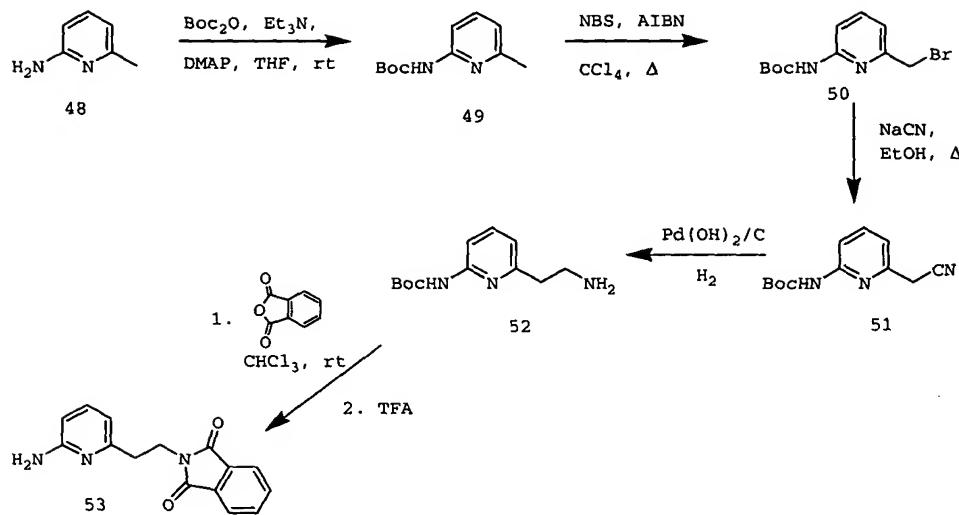
Scheme 13



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Pyridyl-2-thiazoles **47** are prepared as described in Scheme 13. 4-Chloronicotinamide **44** is converted to the thioamide **45** such as by treatment with P_2S_5 , in the presence of base, such as Na_2CO_3 , at a temperature greater than about 10 50°C , and preferably at about reflux. The thioamide **45** is converted to the thiazole ester **46** by treatment with bromoethylpyruvate and heating at a temperature greater than about 50°C , and preferably at about reflux. The ethyl ester is transesterified to the methyl ester with treatment with 15 base, such as NaOMe . Further addition of base and heating at a temperature greater than about 50°C , and preferably at about reflux, hydrolyzed the ester to the acid. Additional NaOMe , in the presence of MeOH , and heating at a temperature greater than about 50°C , and preferably at about reflux, 20 provided the methoxy substituted pyridine compound **47**. Use of other bases and alcohols provide alternative alkoxy substituted compounds.

Scheme 14



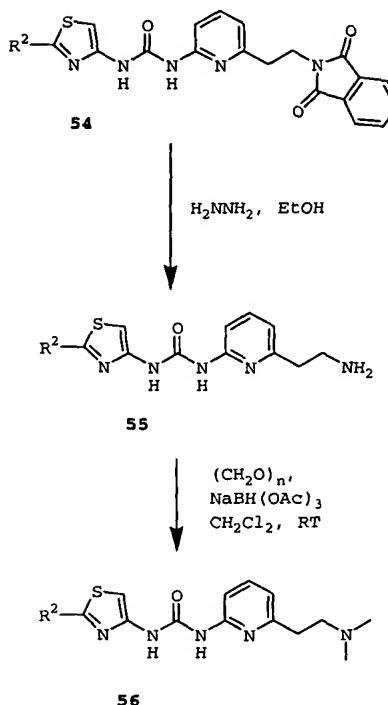
5

Protected aminoalkyl pyridines **53** are prepared from the 2-amino-6-methylpyridine **48** as described in Scheme 14. The amino group of 2-amino-6-methylpyridine **48** is protected, such as with BOC and normal coupling chemistry, such as with **10** Boc_2O and base, like TEA, and DMAP. The protected compound **49** is brominated such as with NBS and AIBN and heating at a temperature greater than about 50°C, and preferably at reflux to provide the bromomethyl derivative **50**. The bromomethyl derivative **50** is converted to the cyanomethyl **15** compound **51** such as with treatment with NaCN in the presence of alcohol solvent such as EtOH, and heating at a temperature greater than about 50°C, and preferably at reflux. The cyanomethyl compound **51** is hydrogenated to the aminoethyl derivative **52** such as with hydrogen in the presence of **20** $\text{Pd}(\text{OH})_2/\text{C}$ at a temperature about RT. The aminoethyl derivative **52** is converted to the di-protected compound such as with phthalic anhydride and heating at a temperature between RT and about 70°C. Upon treatment with

strong acid, such as TFA, provides the 2-aminopyridyl compound **53**.

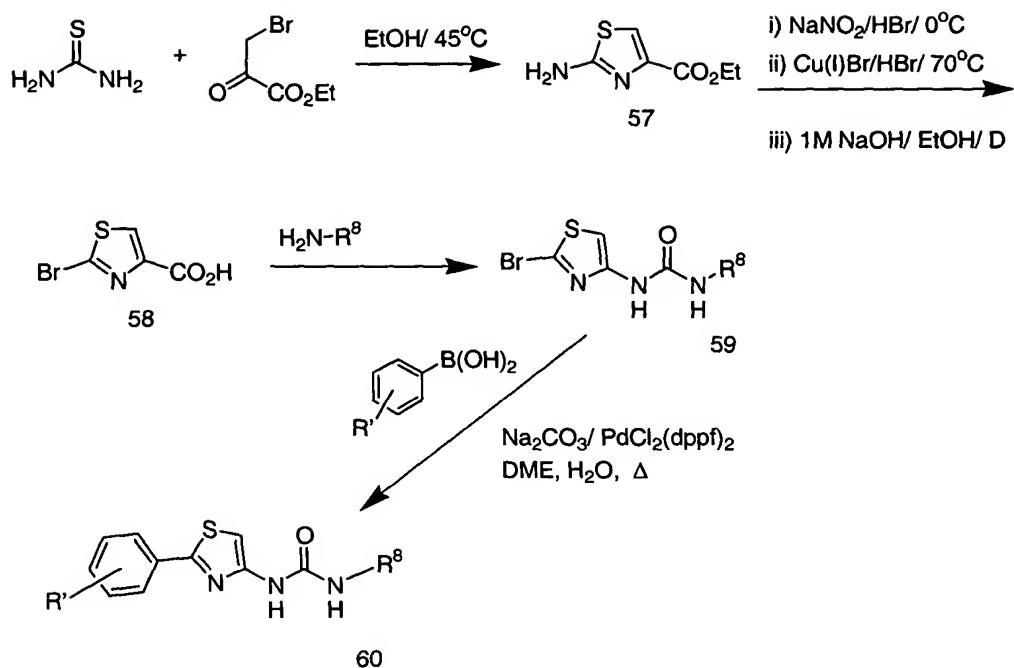
Scheme 15

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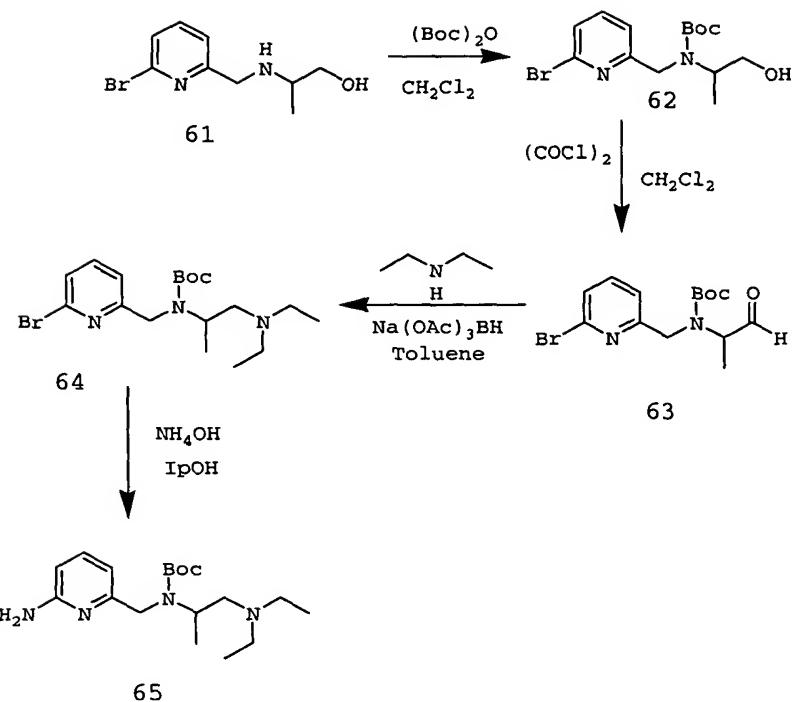
Compounds of Formula I are prepared as described in Scheme 15. Phthalimidylethyl compounds **54** are prepared from the coupling of compounds prepared similar to those described in Scheme 14 and thiazolyl acylazides as described in Scheme 8. Treatment of **54** with hydrazine hydrate and heating at a temperature greater than about 50°C, and preferably at reflux, provides the aminoethyl derivatives **55**. Alkylation of the amine **55**, such as with paraformaldehyde and $\text{NaBH}(\text{OAc})_3$ in a haloalkyl solvent, such as CH_2Cl_2 provides the dimethylamine **56**.

Scheme 16



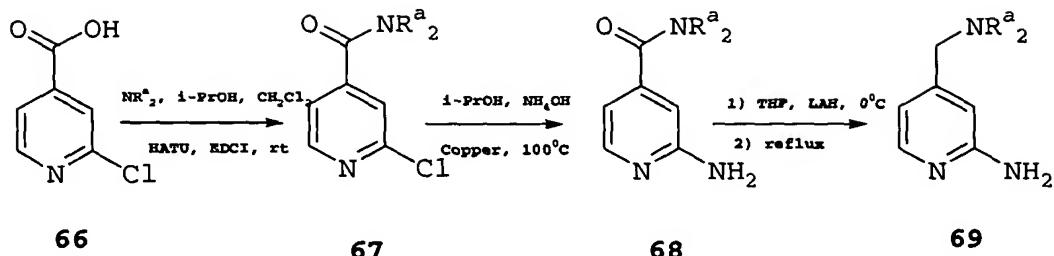
5 Compounds of Formula I (where R^7 is optionally substituted phenyl) are prepared as described in Scheme 16. The 2-aminothiazole **57** is prepared from thiourea and ethyl bromopyruvate, in an alcoholic solvent like ethanol, at a temperature greater than about RT, and preferably at about 10 45°C . Treatment of the ethyl 2-aminothiazole-4-carboxylate with HBr, NaNO_2 , CuBr and heating at a temperature greater than about 50°C , and preferably at about 70°C , provides the bromothiazole ester. Hydrolysis of the ester, such as with aqueous NaOH and alcohol, such as EtOH and heating at a 15 temperature greater than about 50°C , and preferably at reflux provides the bromothiazole acid **58**. Coupling with substituted amines, similar to that described in Scheme 8, provides the 2-bromothiazolyl urea **59**. Suzuki coupling of 20 2-bromothiazolyl urea **59** with phenyl boronic acids provides the compounds where R^7 is optionally substituted phenyl **60**.

Scheme 17



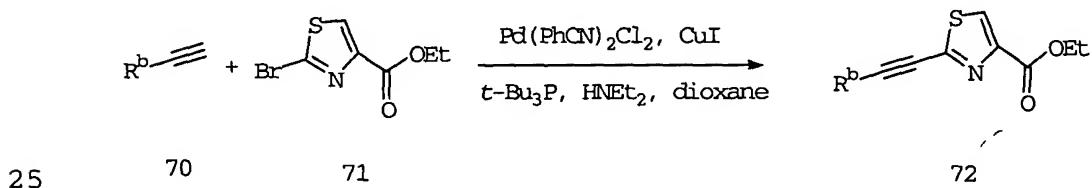
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Substituted aminopyridines **65** are prepared by the method described in Scheme 17. 2-[(6-Bromo-2-pyridyl)methyl]aminopropan-1-ol **61** is protected such as with Boc with di-*tert*-butyldicarbonate in dry CH₂Cl₂. Conversion to the aldehyde **63** is accomplished by treatment with oxalyl chloride (in CH₂Cl₂), and DMSO at a temperature below RT, preferably below about -23°C and more preferably at about -63°C. Addition of base such as DEA, to the aldehyde **63**, and heating to reflux in a Dean-Stark trap, followed by the addition of a solution of NaBH(OAc)₃ in acid such as AcOH at RT provided the aminoalkyl-aminoalkyl derivative **64**. The aminopyridine **65** is prepared as described above.

Scheme 18

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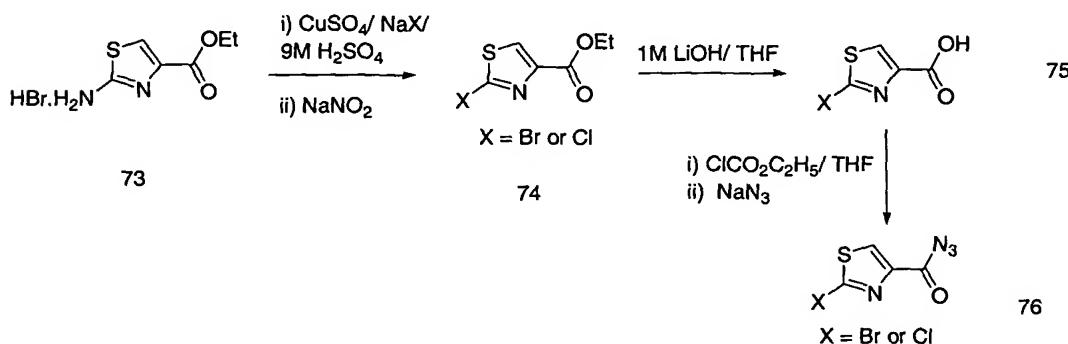
Substituted aminopyridines **69** are prepared by the method described in Scheme 18. 2-Chloroisonicotinic acid **66** is coupled with an amine, such as with standard coupling chemistry, for example with a carbodiimide, such as EDCI, in the presence of base, such as DIEA, in an appropriate solvent such as CH_2Cl_2 , to provide amide **67** where R^a is alkyl, aryl or together with the nitrogen atom forms a heterocyclic ring. The nicotinamide is aminated, such as with ammonium hydroxide in the presence of a metal such as Cu in an appropriate solvent such as $i\text{PrOH}$ and heated at a temperature above RT, preferably above about 50°C , more preferably at about 100°C , preferably in a sealed tube vessel, to form the amino-nicotinamide **68**. The amino-nicotinamide **68** is reduced, such as with LAH, at a temperature above RT, preferably above about 50°C , more preferably at about reflux, to form the methylamine **69**.

Scheme 19

Substituted alkynyl thiazoles **72** are prepared by the method outlined in Scheme 19 where R^b is cycloalkyl, alkyl and the like. Bromothiazole **71** is substituted with the alkyne **70**, such as in the presence of Pd(PhCN)₂Cl₂, CuI₂ and 5 t-Bu₃P, and base such as DEA, in an appropriate solvent such as dioxane. The reaction temperature is maintained at about RT, to form the alkynyl thiazoles **72**.

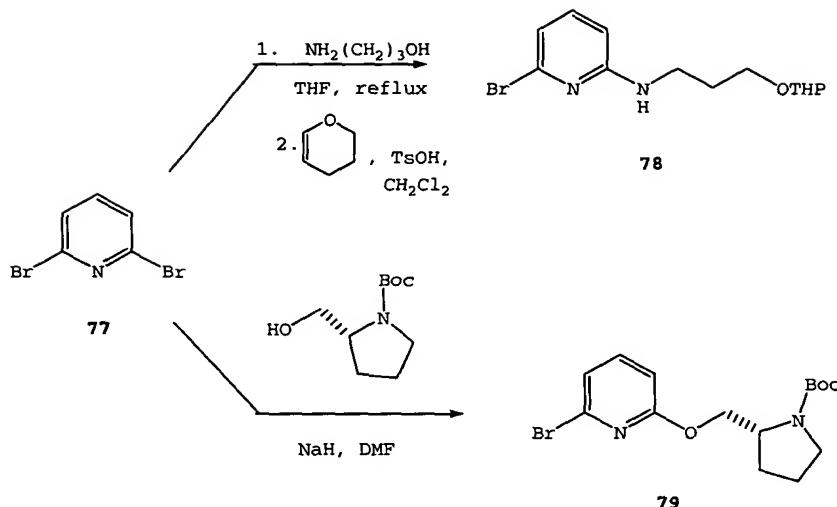
Scheme 20

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Thiazolylazides **76** are prepared by the method shown in Scheme 20. 2-Amino-thiazole-4-carboxylic acid ester hydrobromide is basified, such as with a saturated solution of NaHCO₃, to provide the free base. The free base is subsequently halogenated, such as with a metal halide, preferably NaCl or NaBr, in the presence of acid, preferably H₂SO₄, more preferably 9M H₂SO₄, and CuSO₄ and NaNO₂ at a 15 temperature of about RT to form the halothiazole. The 2-halothiazole-4-carboxylic acid ester is hydrolyzed with a base, such as LiOH, at a temperature above RT, preferably above about 50°C, more preferably about 65°C, to form acid 20 **75**. The azido-thiazole **76** is prepared from the 2-halo-thiazole-4-carboxylic acid **75** in the presence of base, such 25 as TEA, ethyl chloroformate and sodium azide at a temperature about RT.

Scheme 21



5

Substituted bromo-pyridines **78** and **79** are prepared from dibromopyridine **77** as described in Scheme 21. 2,6-Dibromopyridine **77** is reacted with an aminoalcohol in an appropriate solvent, such as THF, at a temperature above RT, preferably at a temperature above about 50°C, more preferably at reflux, to form the amino pyridine. The alcoholamino-pyridine is coupled with 3,4-dihydro-2H-pyran such as with TsOH in the presence of an appropriate solvent, such as CH_2Cl_2 at a temperature of about RT, to form the pyran substituted pyridine **78**.

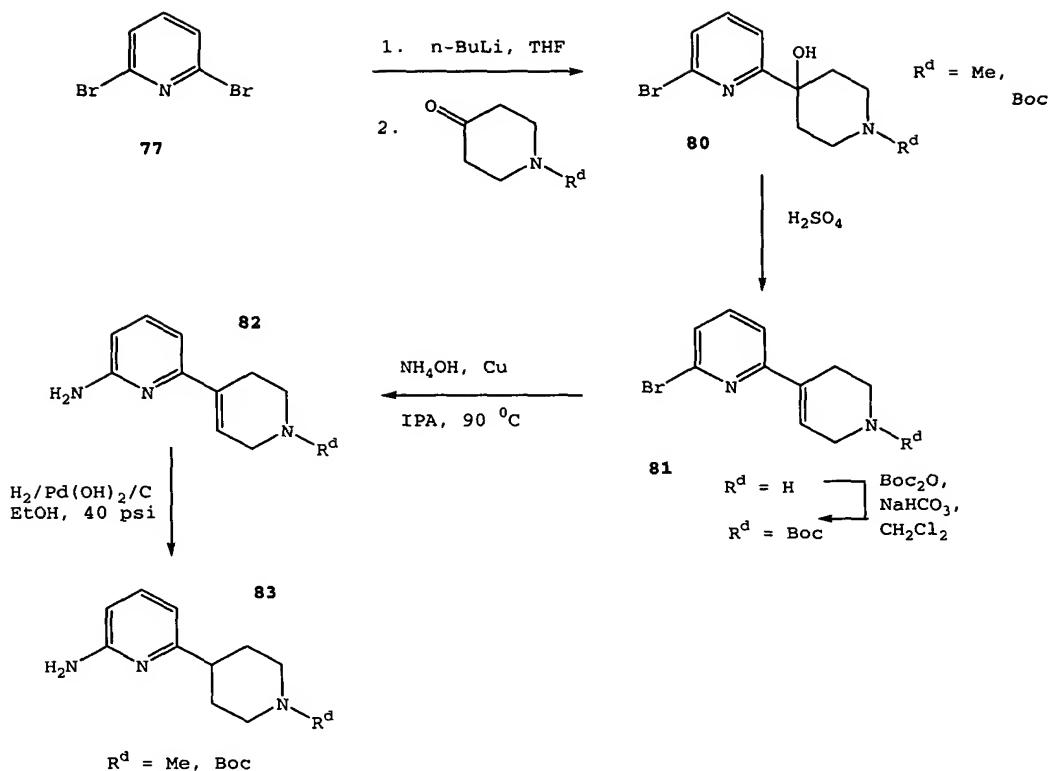
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D-2-Hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester is treated with a strong base, preferably NaH , at a temperature about RT, then 2,6-dibromopyridine **77** is added and reacted at a temperature above RT, preferably at a temperature above about 50°C, more preferably at about 90°C to form the pyrrolidinyl ether **79**.

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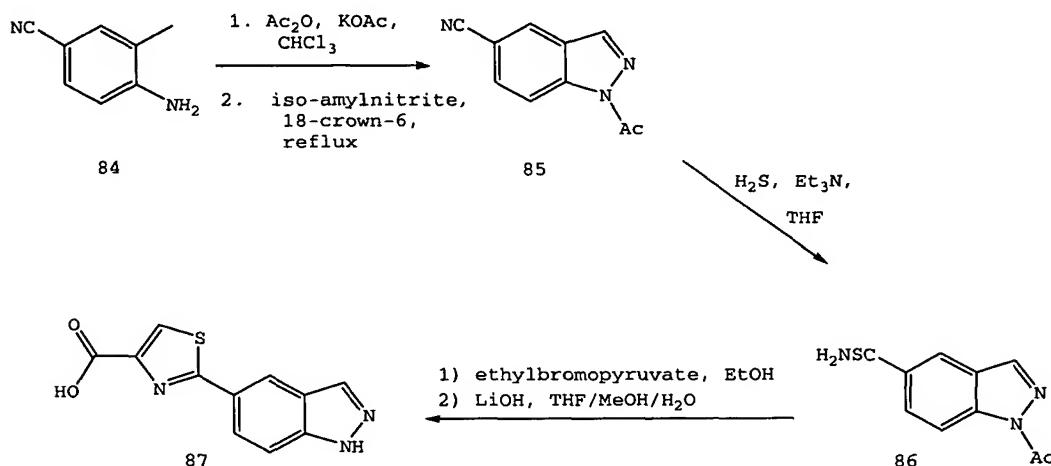
Scheme 22



5 2-(Piperidinyl)pyridines **83** are prepared as described in Scheme 22. Strong base, such as *n*-BuLi, in a solvent such as dry THF, is added to dibromopyridine **77** at a temperature less than RT, preferably below about -50°C, more preferably at about -70°C. 4-Methylpiperidone is added to form the 4-hydroxy-piperidine **80** at a temperature less than RT, preferably below about -50°C, more preferably at about -70°C. The 4-hydroxy piperidine **80** is hydrated, such as with strong acid, preferably *H*₂SO₄, at a temperature above RT, preferably above 75°C, more preferably at about 100°C, to 10 form the tetrahydro-bipyridine **81**. The 2-bromo-pyridine **81** is aminated, such as with NH₄OH, in the presence of Cu powder at a temperature above RT, preferably above about 75°C, more preferably at about 100°C, to form the amino- 15

pyridine **82**. Preferably the reaction is run in a sealed tube. The 1',2,3',6'-tetrahydroy-[2,4']bipyridinyl-6-ylamine is hydrogenated, such as with H₂ in the presence of Pd(OH)₂/C, at a temperature of about RT, to form the 5 piperidinyl pyridine **83**.

Scheme 23



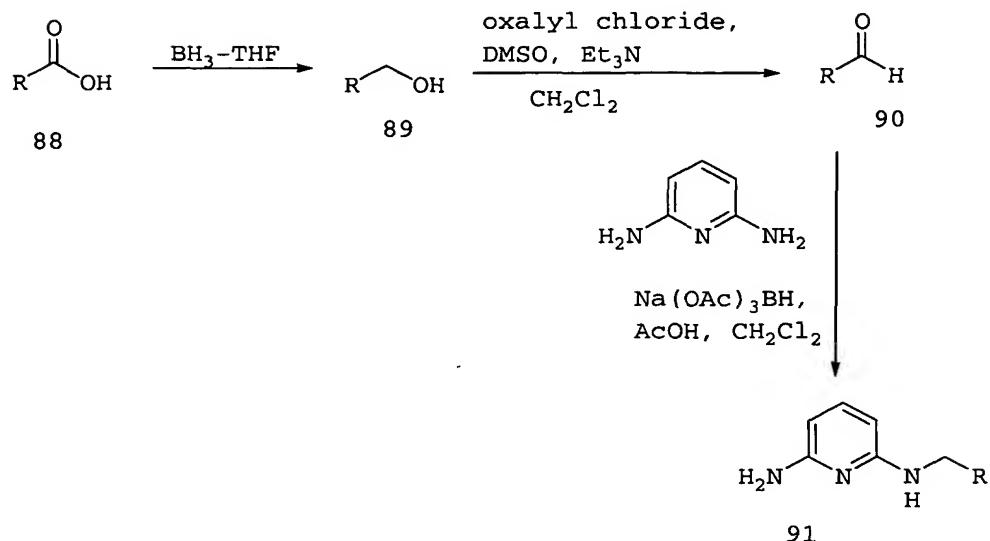
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Thiazolyl indazoles **87** can be prepared from anilines as outlined in Scheme 23. Similar to the method of J. Sun, et al, J.Org.Chem., 1997, p. 5627, protected 1H-indazole-5-carbonitrile **85** is prepared from 4-amino-3-methylbenzonitrile **84** in the presence of acetic anhydride, and KOAc in an appropriate solvent such as CHCl₃. The protected 1H-indazole-5-carbothioic acid amide **85** is prepared from the carbonitrile **84** by treatment with H₂S gas in the presence of base, such as Et₃N and solvent, such as THF, at a 15 temperature below RT, preferably at about 0°C. The amide **86** is added to a diketo compound, such as ethylbromopyruvate at a temperature above RT, preferably above about 50°C, more 20 preferably at reflux, in an appropriate solvent such as EtOH, to form the thiazolyl indazole ester. The ester is 25 hydrolyzed with base, such as with LiOH at a temperature of

about RT to yield the free acid **87**. Additionally, the indazole may be acylated, such as with Ac_2O .

Scheme 24

5



Disubstituted aminopyridines **91** can be prepared from the corresponding acids **88**, where R^c is heterocyclic, as described in Scheme 24. Carboxylic acid or the corresponding ester is reduced, such as with $\text{BH}_3\text{-THF}$ solution in a solvent, such as in dry THF, at a temperature of about RT, to form the alcohols **89**. Oxalyl chloride and DMSO in a solvent such as dry CH_2Cl_2 , is treated with the alcohol **89** in the presence of base, such as TEA at a temperature of about RT, to form the aldehyde **90**. The aldehyde **90** is coupled with an heteroaryl group, such as diaminopyridine in a solvent such as dry CH_2Cl_2 , via reductive amination for example in the presence of $\text{NaBH}(\text{OAc})_3$, piperidine and HOAc , at a temperature above RT, preferably at about 40°C , to form the substituted amino pyridine **91**.

N-Oxides can be obtained in a known matter by reacting a compound of Formula I-VI with hydrogen peroxide or a peracid, e.g. 3-chloroperoxy-benzoic acid, in an inert solvent, e.g. CH_2Cl_2 , at a temperature between about -10 to 5 about 35°C, such as about 0°C to about RT.

In the preparation of starting materials, existing functional groups, for example carboxy, hydroxy, amino, or mercapto, which do not participate in the reaction should, if necessary, be protected. Such protecting groups are 10 those or similar to those usually used in the synthesis of peptide compounds, cephalosporins, penicillins, nucleic acid derivatives or sugars. Preferred protecting groups, their introduction and their removal are described above or in the examples.

15 The protecting groups may already be present in precursors and should protect the functional groups concerned against unwanted secondary reactions, such as acylations, etherifications, esterifications, oxidations, solvolysis, and similar reactions. It is a characteristic of 20 protecting groups that they lend themselves ready removal, i.e. without undesired secondary reactions, typically by solvolysis, reduction, photolysis or also by enzyme activity, for example under conditions analogous to physiological conditions, and that they are not present in 25 the end-products. One skilled in the art knows, or can easily establish, which protecting groups are suitable with the reactions mentioned above and hereinafter.

The protection of such functional groups by such 30 protecting groups, the protecting groups themselves, and their removal reactions are described for example in standard reference works, such as J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London and New York 1973, in T. W. Greene, "Protective Groups in Organic Synthesis", Wiley, New York 1981, in "The

Peptides"; Volume 3 (editors: E. Gross and J. Meienhofer), Academic Press, London and New York 1981, in "Methoden der organischen Chemie" (Methods of organic chemistry), Houben Weyl, 4th edition, Volume 15/1, Georg Thieme Verlag, Stuttgart 1974, in H.-D. Jakubke and H. Jescheit, "Aminosäuren, Peptide, Proteine" (Amino acids, peptides, proteins), Verlag Chemie, Weinheim, Deerfield Beach, and Basel 1982, and in Jochen Lehmann, "Chemie der Kohlenhydrate: Monosaccharide und Derivate" (Chemistry of carbohydrates: monosaccharides and derivatives), Georg Thieme Verlag, Stuttgart 1974.

In the additional process steps, carried out as desired, functional groups of the starting compounds which should not take part in the reaction may be present in unprotected form or may be protected for example by one or more of the protecting groups mentioned above under "protecting groups". The protecting groups are then wholly or partly removed according to one of the methods described there.

In certain cases, typically in hydrogenation processes, it is possible to achieve stereoselective reactions, allowing for example easier recovery of individual isomers.

The solvents from which those can be selected which are suitable for the reaction in question include, for example, water, esters, typically lower alkyl-lower alkanoates, e.g. EtOAc, ethers, typically aliphatic ethers, e.g. Et₂O, or cyclic ethers, e.g. THF, liquid aromatic hydrocarbons, typically benzene or toluene, alcohols, typically MeOH, EtOH or 1-propanol or iPrOH, nitriles, typically CH₃CN, halogenated hydrocarbons, typically CH₂Cl₂, acid amides, typically DMF, bases, typically heterocyclic nitrogen bases, e.g. pyridine, carboxylic acids, typically lower alkanecarboxylic acids, e.g. AcOH, carboxylic acid

anhydrides, typically lower alkane acid anhydrides, e.g. Ac₂O, cyclic, linear, or branched hydrocarbons, typically cyclohexane, hexane, or isopentane, or mixtures of these solvents, e.g. aqueous solutions, unless otherwise stated in 5 the description of the process.

The invention relates also to those forms of the process in which one starts from a compound obtainable at any stage as a transient and carries out the missing steps, or breaks off the process at any stage, or forms a starting 10 material under the reaction conditions, or uses said starting material in the form of a reactive derivative or salt, or produces a compound obtainable by means of the process according to the invention and processes the said compound *in situ*. In the preferred embodiment, one starts 15 from those starting materials which lead to the compounds described above as preferred.

The compounds of Formula I-VI, including their salts, are also obtainable in the form of hydrates, or their crystals can include for example the solvent used for 20 crystallization (present as solvates).

New starting materials and/or intermediates, as well as processes for the preparation thereof, are likewise the subject of this invention. In the preferred embodiment, such starting materials are used and reaction conditions so 25 selected as to enable the preferred compounds to be obtained.

Starting materials of the invention, are known, are commercially available, or can be synthesized in analogy to or according to methods that are known in the art.

30 All remaining starting materials are known, capable of being prepared according to known processes, or commercially obtainable; in particular, they can be prepared using processes as described above or as in the examples.

The compounds of this invention may contain one or more asymmetric centers and thus occur as racemates and racemic mixtures, scalemic mixtures, single enantiomers, individual diastereomers and diastereomeric mixtures. All 5 such isomeric forms of these compounds are expressly included in the present invention.

The compounds of this invention may also be represented in multiple tautomeric forms, for example, as illustrated below:

10



The invention expressly includes all tautomeric forms of the compounds described herein.

15 The compounds may also occur in cis- or trans- or E- or Z- double bond isomeric forms. All such isomeric forms of such compounds are expressly included in the present invention. All crystal forms of the compounds described herein are expressly included in the present invention.

20 Substituents on ring moieties (e.g., phenyl, thiazolyl, etc.) may be attached to specific atoms, whereby they are intended to be fixed to that atom, or they may be drawn unattached to a specific atom, whereby they are intended to be attached at any available atom that is not 25 already substituted by an atom other than H (hydrogen).

The compounds of this invention may contain heterocyclic ring systems attached to another ring system. Such heterocyclic ring systems may be attached through a carbon atom or a heteroatom in the ring system.

30 A compound of any of the formulas delineated herein may be synthesized according to any of the processes

delineated herein. In the processes delineated herein, the steps may be performed in an alternate order and may be preceded, or followed, by additional protection/deprotection steps as necessary. The processes may further comprise use

5 of appropriate reaction conditions, including inert solvents, additional reagents, such as bases (e.g., LDA, DIEA, pyridine, K_2CO_3 , and the like), catalysts, and salt forms of the above. The intermediates may be isolated or carried on *in situ*, with or without purification.

10 Purification methods are known in the art and include, for example, crystallization, chromatography (liquid and gas phase, simulated moving bed ("SMB")), extraction, distillation, trituration, reverse phase HPLC and the like. Reactions conditions such as temperature, duration,

15 pressure, and atmosphere (inert gas, ambient) are known in the art and may be adjusted as appropriate for the reaction. Additionally, the compounds can be produced metabolically.

As can be appreciated by one skilled in the art, the above synthetic schemes are not intended to comprise a

20 comprehensive list of all means by which the compounds described and claimed in this application may be synthesized. Further methods will be evident to those of ordinary skill in the art. Additionally, the various synthetic steps described above may be performed in an

25 alternate sequence or order to give the desired compounds. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the inhibitor compounds described herein are known in the art and include, for example, those such as

30 described in R. Larock, *Comprehensive Organic Transformations*, VCH Publishers (1989); T. Greene and P. Wuts, *Protective Groups in Organic Synthesis*, 3rd. Ed., John Wiley and Sons (1999); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons

(1994); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995); P. Lopez et al., *Synthesis* 2, 186 (1998); A. Mikhalev, et al., Khim. Geterotsikl Soedin, 5, 697 (1997); M. Fernandez, et al., 5 *Synthesis*, 11, 1362 (1995); P. Desos, et al., *J. Med. Chem.*, 39, 197 (1996); G. Timari, et al., *Synlett*, 9, 1067 (1997); Y. Tagawa, et al., *J. Heterocycl. Chem.*, 34, 1677 (1997); A. Fuerstner, et al., *Chem. Sci.* 50, 326 (1995); A. Katritzky and A. Pozharski, *Handbook of Heterocyclic Chemistry*, 2nd 10 Ed. (2001); and WO01/132658.

The compounds of this invention may be modified by appending appropriate functionalities to enhance selective biological properties. Such modifications are known in the art and include those which increase biological penetration 15 into a given biological compartment (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion.

The following examples contain detailed descriptions 20 of the methods of preparation of compounds of Formulas I-VI. These detailed descriptions fall within the scope, and serve to exemplify, the above described General Synthetic Procedures which form part of the invention. These detailed 25 descriptions are presented for illustrative purposes only and are not intended as a restriction on the scope of the invention. All parts are by weight and temperatures are in Degrees centigrade unless otherwise indicated. All compounds showed NMR spectra consistent with their assigned structures.

The following abbreviations are used:

	AcOH, HOAc -	acetic acid
	Ac ₂ O -	acetic anhydride
5	AcCN, CH ₃ CN -	acetonitrile
	ATP -	adenosine triphosphate
	NH ₃ -	ammonia
	NH ₄ OH -	ammonium hydroxide
	NH ₄ Cl -	ammonium chloride
10	AIBN -	2,2'-azobis-isobutyrlnitrile
	HATU -	O-(7-azabenzotriazol-1-yl)-N,N,N',N'- tetramethyluronium hexafluorophosphate
	BOP-Cl -	bis(2-oxo-3-oxazolidinyl)phosphinic chloride
15	PdCl ₂ (dppf) -	1,1-bis(diphenylphosphino)ferrocene palladium chloride
	BH ₃ -THF -	borane-tetrahydrofuran
	BSA -	bovine serum albumin
	BOC -	tert-butyloxycarbonyl
20	BuLi -	n-butyllithium
	Boc ₂ O -	di-tert-butyl dicarbonate, BOC anhydride
	CCl ₄ -	carbon tetrachloride
	CHCl ₃ -	chloroform
	Cu -	copper
25	CuBr-	copper(I) bromide
	CuI ₂ -	copper(II) iodide
	CuSO ₄ -	copper(II) sulfate
	CH ₂ Cl ₂ -	dichloromethane, methylene chloride
	Pd(PhCN) ₂ Cl ₂ -	dichlorobis(benzonitrile)palladium
30	DEA, Et ₂ NH -	diethylamine
	Et ₂ O -	diethyl ether
	DIEA -	diisopropylethylamine
	DIBAL-H -	diisobutylaluminum hydride
	DME -	1,2-dimethoxyethane

	EDC, EDCI -	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
	DMAP -	4-(dimethylamino)pyridine
	DMF -	dimethylformamide
5	DMSO -	dimethylsulfoxide
	DPPA, $(\text{PhO})_2\text{PON}_3$ -	diphenylphosphoryl azide
	DTT -	dithiothreitol
	EtOH -	ethanol
	EtOAc -	ethyl acetate
10	EGTA -	ethylene glycol-bis(β -aminoethyl ether)-N,N,N',N'-tetraacetic acid
	EDTA -	ethylenediaminetetraacetic acid
	g -	gram
	h -	hour
15	HCl -	hydrochloric acid
	HBr -	hydrobromic acid
	H ₂ S -	hydrogen sulfide
	HOEt -	hydroxybenzotriazole
	IpOH -	isopropanol
20	LAH, LiAlH ₄ -	lithium aluminum hydride
	LiOH -	lithium hydroxide
	MgCl ₂ -	magnesium chloride
	MgSO ₄ -	magnesium sulfate
	MnCl ₂ -	manganese chloride
25	MeOH -	methanol
	MeMgI -	methyl magnesium iodide
	mg -	milligram
	ml, mL -	milliliter
	min -	minutes
30	NBS -	N-bromosuccinimide
	N ₂ -	nitrogen
	Pd(OH) ₂ /C -	palladium hydroxide on carbon
	H ₃ PO ₄ -	phosphoric acid
	P ₂ S ₅ -	phosphorous pentasulfide

	PtO ₂ -	platinum oxide
	KOAc -	potassium acetate
	KOH -	potassium hydroxide
	pyr -	pyridine
5	RT -	room temperature
	Na ₂ SO ₄	sodium sulfate
	Na ₂ CO ₃	sodium carbonate
	NaCNBH ₃ -	sodium cyanoborohydride
	NaBH ₄ -	sodium borohydride
10	NaOH -	sodium hydroxide
	NaOEt	sodium ethoxide
	NaOMe	sodium methoxide
	NaBr -	sodium bromide
	NaCl -	sodium chloride
15	NaCN -	sodium cyanide
	NaNO ₂ -	sodium nitrite
	NaN ₃ -	sodium azide
	SOV -	sodium orthovanadate
	NaBH(OAc) ₃ -	sodium trisacetoxy borohydride
20	NaH -	sodium hydride
	NaHCO ₃ -	sodium bicarbonate
	H ₂ SO ₄ -	sulfuric acid
	THF -	tetrahydrofuran
	TsOH -	Toluenesulfonic acid
25	t-Bu ₃ P -	tri-tert-butylphosphine
	TEA, Et ₃ N -	triethylamine
	TFA -	trifluoroacetic acid
	Tris-HCl -	Tris(hydroxymethyl)aminomethane hydrochloride salt
30	H ₂ O -	water

Preparation A: 2-Amino-6-morpholinopyridine:

A mixture of 2-chloro-6-aminopyridine (200 mg, 1.49 mmol), morpholine (326 mg, 3.75 mmol) and phenol (2 g) was

heated at 150°C for 20 h. After cooling to RT, 3N NaOH (10mL) was added and the mixture was extracted with EtOAc (3x50mL). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude was purified by chromatography on silica gel (1:10 MeOH/CH₂Cl₂) to afford the morpholino derivative as an amber oil. MS m/z: 180 (M+1).

Preparation B: 2-Bromo-6-N,N-diethylamidopyridine:

10 Ethyl chloroformate (1.76 g, 16.3 mmol) was added dropwise to a mixture of 6-bromopicolinic acid (3 g, 14.8 mmol) and Et₃N (1.8 g, 17.8 mmol) in THF (150 mL) at 0°C. After the mixture was stirred for 1 h, DEA (1.3 g, 17.8 mmol) was added slowly to the mixture at 0°C. The resulting 15 mixture was stirred at RT for 5 h. H₂O (200 mL) was added and the mixture was extracted with EtOAc (3x120 mL). The combined organic layers were washed with 1N NaOH and brine, dried over Na₂SO₄, and filtered. The filtrate was concentrated *in vacuo* to afford 2-bromo-6-N,N-diethylamidopyridine as an amber oil. MS m/z: 259 (M+1).

Preparation C: 2-Amino-6-N,N-diethylamidopyridine:

A mixture of 2-bromo-6-N,N-diethylamidopyridine (3.5 g), 50 mL of 37% NH₄OH and 0.8 g of Cu powder in 40 mL of 25 IpOH was heated at 100°C in sealed tube for 20 h. After cooling to RT, brine was added and the mixture was extracted with EtOAc (3X120 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo* to afford the amino derivative as a 30 light amber solid. MS m/z: 194 (M+1).

Preparation D: 2-Amino-6-N,N-diethylaminomethylpyridine:

To a solution of 2-amino-6-N,N-diethylamidopyridine (2.2 g, 11.4 mmol) in 200 mL of THF was added slowly 34.2 mL

of LiAlH₄ (1.3 g, 34.2 mmol) solution in Et₂O at 0°C. The resulting mixture was heated at reflux for 6 h. After cooling to 0°C, 2 mL of H₂O, 1.3 mL of 15% NaOH and 7.5 mL of H₂O was added to the mixture sequentially. After stirring 5 for 2 h at RT, the mixture was filtered through Celite®. The filtrate was concentrated and purified by chromatography on silica gel (1:10 MeOH(NH₃)/CH₂Cl₂) to afford the aminomethyl compound as an amber oil. MS m/z: 180 (M+1).

10 **Preparation E: 2-Amino-6-(N-methylpiperazinyl)pyridine:**

A mixture of 2-bromo-6-aminopyridine (3 g, 17.34 mmol), 1-methylpiperazine (2.3 g, 22.54 mmol) and Cu powder (0.5 g, 7.87 mmol) in 5 mL of 2,4-diethylphenol was heated at 150°C for 20 h. After cooling to RT, 3N HCl (30 mL) was 15 added and the mixture was extracted with Et₂O (2x100 mL). The aqueous layer was basified with concentrated NH₄OH to pH>10 and then extracted with EtOAc (3x100 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude was purified 20 by chromatography on silica gel (1:10 MeOH(NH₃)/CH₂Cl₂) to afford the piperazinyl compound as a light amber solid. MS m/z: 193 (M+1).

Preparation F: 2-Amino-6-(4-morpholino)propylamino-pyridine:

25 A mixture of 2-bromo-6-aminopyridine (0.5 g, 2.92 mmol), 4-(3-aminopropyl)morpholine (1.5 g 10.42 mmol) and Cu powder (0.6 g, 9.52 mmol) in 15 mL of IpOH and 5 mL of H₂O was heated at 100°C in a sealed tube for 24 h. After cooling to RT, water was added and the mixture was extracted with 30 EtOAc (3X50 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude was purified by chromatography on silica gel (1:10 MeOH(NH₃)/CH₂Cl₂) to afford the morpholino compound as an amber oil. MS m/z: 237 (M+1).

Prparation G: 2-Amino-6-(2-N,N-dimethylamino)ethylaminopyridine:

A mixture of 2-bromo-6-aminopyridine (0.3 g, 1.17 mmol), N,N-dimethylethylenediamine (1 g, 11.36 mmol) and Cu powder (0.74 g, 11.7 mmol) in 30 mL of IpOH was heated at 100°C in sealed tube for 20 h. After cooling to RT, H₂O was added and the mixture was extracted with EtOAc (3x50 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo. The crude was purified by chromatography on silica gel (1:10 MeOH (NH₃) / CH₂Cl₂) to afford the compound as an oil. MS m/z: 181 (M+1).

15 Preparation H: Amino-2-pyridylmethane-1-thione:

2-Cyanopyridine (2.6 g, 0.025 mol) was added to a solution of TEA (5.5 mL) and dry pyridine (50 mL) at RT. H₂S was bubbled through the solution for 1 h. Afterwards, H₂O (150 mL) was added and the mixture was extracted with EtOAc (3x50mL). The EtOAc extracts were dried over Na₂SO₄, filtered, and the solvent was removed under vacuum. The resulting residue was purified by column chromatography eluting with hexanes:EtOAc (4:1) to give amino-2-pyridylmethane-1-thione as a light yellow solid. GC/MS m/z: 139 (M+H); GC Retention time: 7.93 min.

Preparation I: 2-(2-Pyridinyl)thiazole-4-carboxylic acid:

Amino-2-pyridylmethane-1-thione (1.88 g, 0.0136 mol), ethyl bromopyruvate (1.80 mL, 0.0143 mol) and EtOH (30 mL) were combined and heated to reflux. GC/MS of reaction mixture after 3 h showed total consumption of the starting materials. After cooling to RT, the solvent was removed under vacuum resulting in a dark brown oil (GC/MS m/z: 235 (M+H); GC Retention time: 10.69 min). The material was

taken up in MeOH (20 mL), 1.0M LiOH-H₂O (20 mL) was added and the mixture was heated to 100°C for 14 h. After cooling to RT, the excess MeOH was evaporated and the resulting brown solid filtered. The material was washed with a 5 minimum of H₂O and dried *in vacuo* to give the thiazole as a brown solid.

10 **Preparation J: 2-(4-Pyridinyl)-4-thiazolylcarbonylazide:**

To a suspension of 2-(4-pyridinyl)-4-thiazolyl carboxylic acid (Maybridge Chem., 6.0 g, 29.1 mmol) in 150 mL MeOH at RT was added NaOH (1.28 g, 32.0 mmol) and the mixture was stirred at RT for 45 min. The reaction mixture 15 was concentrated *in vacuo* then dried under high vacuum for 60 h (overnight drying is a minimum). The crude salt was suspended in 150 mL of CH₂Cl₂ and cooled in an ice bath. Oxalyl chloride (2.8 mL) was added slowly to the suspension followed by a catalytic amount of DMF (0.2 mL). The mixture 20 was stirred for 2 h and warmed to RT. The reaction was cooled in an ice bath and a solution of NaN₃ (2.27 g) in water (90 mL) was added and stirring was continued for 3 h. The reaction mixture was diluted with water (90 mL) and extracted with CH₂Cl₂ (3x75mL). The combined organic layers 25 were filtered through Celite® (~12 g) washed with 90 mL brine, dried with MgSO₄ and concentrated *in vacuo*. Drying the crude compound on the vacuum line afforded the azido derivative as a light brown solid. MS *m/z*: 204.5 (M-N₂+H).

30 **Preparation K: 2-(3-Pyridinyl)-4-thiazolylcarbonylazide:**

In a manner similar to that described for the preparation of 2-(4-pyridinyl)-4-thiazolylcarbonylazide, 6.0 g of 2-(3-pyridinyl)-4-thiazolylcarboxylic acid was treated successively with NaOH, oxalyl chloride and a solution of

NaN_3 in water to give the 3-pyridinylazide as a pale brown solid. MS m/z : 204.5 ($\text{M-N}_2+\text{H}$).

Preparation L: 2-(2-Pyridinyl)-4-thiazolylcarbonylazide:

5 In a manner similar to that described for the preparation of 2-(4-pyridinyl)-4-thiazolyl-carbonylazide, 2-(2-pyridinyl)-4-thiazolylcarboxylic acid (1.0 g) was treated successively with NaOH , oxalyl chloride and a solution of NaN_3 in water to give the 2-pyridinyl azide as a 10 pale brown solid: m.p. 112-114°C. MS m/z : 232 ($\text{M}+\text{H}$).

Preparation M: 2-Phenyl-4-thiazolylcarbonylazide:

In a manner similar to that described for the preparation of 2-(4-pyridinyl)-4-thiazolylcarbonyl-azide, 15 1.0 g of 2-phenyl-4-thiazolylcarboxylic acid was treated successively with NaOH , oxalyl chloride and a solution of NaN_3 in water to give the phenylazide as an off white solid. MS m/z : 203.5 ($\text{M-N}_2+\text{H}$).

20 **Preparation N: 4-(6-Bromo-pyridin-2-ylmethyl)-morpholine**

To a stirred solution of 6-bromo-2-pyridine-carboxaldehyde (200 mg, 1.08 mmol) in dichloroethane (10 mL) was added morpholine (0.14 mL, 1.62 mmol) followed by NaBH(OAc)_3 (458 mg, 2.16 mmol) and AcOH (0.25 mL, 4.32 mmol). The resulting mixture was stirred at RT for 12 h. The reaction was quenched with 2M Na_2CO_3 solution and stirred 1 h. The mixture was poured into Et_2O and washed with 2 M Na_2CO_3 solution. The organic layer was collected, dried over Na_2SO_4 and concentrated in vacuo to give 2-bromo-30 6-morpholinyl-methylpyridine as a white solid. MS m/z : 256.9 ($\text{M}+\text{H}$).

The following compounds were prepared in a manner similar to that described above:

1] 1-(6-Bromopyridin-2-ylmethyl)-piperidine-4-carboxylic acid ethyl ester, as a pale yellow solid, was prepared in a manner similar to that described in General Preparation N [6-bromo-2-pyridinecarboxaldehyde (400 mg, 2.16 mmol) was added to ethyl isonipecotate (0.5 mL, 3.24 mmol) in dry CH_2Cl_2 (10 mL)]. MS m/z: 327.0 (M+H). Calc'd for $\text{C}_{14}\text{H}_{19}\text{BrN}_2\text{O}_2$: 326.90.

5

10

2] To 6-bromo-2-pyridinecarboxaldehyde (400 mg, 2.16 mmol) was added L-leucinol (0.42 mL, 3.24 mmol) in dry CH_2Cl_2 (10 mL) to give 2-[(6-bromo-pyridin-2-ylmethyl)-amino]-4-methyl-pentan-1-ol as brown solid. MS m/z: 287.6 (M+H). Calc'd for $\text{C}_{12}\text{H}_{19}\text{BrN}_2\text{O}$: 287.2.

15

20

3] To 6-bromo-2-pyridinecarboxaldehyde (500 mg, 2.69 mmol) was added 1,4-dioxa-8-azaspiro-[4,5]-decane (0.5 mL, 4.03 mmol) in dry CH_2Cl_2 (10 mL) to give 2-bromo-6-(4-ethoxyacetal)-piperidinylmethylpyridine as white solid. MS m/z: 313 (M+H). Calc'd for $\text{C}_{13}\text{H}_{17}\text{BrN}_2\text{O}_2$: 313.2.

25

30

4] To 6-bromo-2-pyridinecarboxaldehyde (400 mg, 2.15 mmol) was added 3,5-dimethylpiperidine (0.4 mL, 3.22 mmol) in dry CH_2Cl_2 (10 mL) to give 2-bromo-6-(3,5-dimethyl)piperidinylmethyl pyridine as white solid. MS m/z: 283.2 (M+H). Calc'd for $\text{C}_{13}\text{H}_{19}\text{BrN}_2$: 283.2

5] To 6-bromo-2-pyridinecarboxaldehyde (400 mg, 2.15 mmol) was added 4-methylpiperidine (0.4 mL, 3.22 mmol) in dry CH_2Cl_2 (10 mL) to give 2-bromo-6-[(4-

methyl)piperidinylmethyl]pyridine as a white solid.
MS m/z: 269.4 (M+H). Calc'd for C₁₂H₁₇BrN₂: 269.18.

6] To 6-bromo-2-pyridinecarboxaldehyde (400 mg, 2.15
5 mmol) was added 2-methylpiperidine (0.4 mL, 3.22
mmol) in dry CH₂Cl₂ (10 mL) to give 2-bromo-6-[(2-
methylpiperidinyl)methyl]pyridine as a pale yellow
solid. MS m/z: 269.1 (M+H). Calc'd for C₁₂H₁₇BrN₂:
269.18.

10
7] To 6-bromo-2-pyridinecarboxaldehyde (400 mg, 2.15
mmol) was added 4-(1-pyrrolidinyl)-piperidine (500
mg, 3.22 mmol) in dry CH₂Cl₂ (15 mL) to give 2-
bromo-6-[4-(1-pyrrolidinyl)-
15 piperidinylmethyl]pyridine as a pale yellow solid.
MS m/z: 326.1 (M+2H). Calc'd for C₁₅H₂₂BrN₃: 324.26.

20
8] To 6-bromo-2-pyridinecarboxaldehyde (400 mg, 2.15
mmol) was added 3-hydroxypiperidine (326 mg, 3.22
mmol) in dry CH₂Cl₂ (15 mL) to give 2-bromo-6-(3-
hydroxypiperidinyl)methyl pyridine as pale yellow
solid. MS m/z: 271.2 (M+H). Calc'd for C₁₁H₁₅BrN₂O:
271.15.

25
9] To 6-bromo-2-pyridinecarboxaldehyde (300 mg, 1.62
mmol) was added hexamethyleneimine (0.27 mL, 2.43
mmol) in dry CH₂Cl₂ (10 mL) to give 2-bromo-6-
(azaperhydroepinylmethyl)pyridine as a white solid.
MS m/z: 270.3 (M+H). Calc'd for C₁₂H₁₇BrN₂: 269.18.

30
10] To 4-hydroxypiperidine (143 mg, 1.41 mmol) was
added a solution of 6-bromo-2-pyridine-
carboxaldehyde (200 mg, 1.08 mmol) to give 2-bromo-
6-[(4-hydroxypiperidyl)methyl]-pyridine as a white

solid. MS *m/z*: 271.0 (M+H). Calc'd for C₁₁H₁₅BrN₂O - 271.15.

11] 3-Hydroxypropylamine (0.15 mL, 2.02 mmol) was
5 added to a solution of 6-bromo-2-pyridine-
carboxaldehyde (250 mg, 1.35 mmol) to give 2-bromo-
6-[(3-hydroxypropyl)amino]-methylpyridine as a
white solid. MS *m/z*: 245.1 (M+H). Calc'd for
C₁₁H₁₃BrN₂O - 245.19.

10 12] Ethyl(piperidyl-3-carboxylate (0.92 mL, 5.92 mmol)
was added to a solution of 6-bromo-2-
pyridinecarboxaldehyde (1.0 g, 5.38 mmol) to give
ethyl 1-[(6-bromopyridin-2-yl)methyl]-piperidine-3-
15 carboxylate as a colorless oil. MS *m/z*: 327.1
(M+H). Calc'd for C₁₄H₁₉BrN₂O₂ - 327.22.

20 13] Ethyl (2-piperidyl)carboxylate (0.92 mL, 5.92
mmol) was added to a solution of 6-bromo-2-
pyridinecarboxaldehyde (1.0 g, 5.38 mmol) to give
ethyl 1-[(6-bromopyridin-2-yl)methyl]-piperidine-2-
carboxylate as a colorless oil). MS *m/z*: 327.1
(M+H). Calc'd for C₁₄H₁₉BrN₂O₂ - 327.22.

25 14] N,N-Diethylcarbamoyl-piperidine-3-carboxamide
(0.92 mL, 5.92 mmol) was added to a solution of 6-
bromo-2-pyridinecarboxaldehyde (1.0 g, 5.38 mmol)
to give N,N-diethyl 1-(6-bromopyridin-2-
ylmethyl)piperidine-3-carboxamide as a colorless
30 oil. MS *m/z*: 354.1 (M+H). Calc'd for C₁₆H₂₄BrN₃O -
354.29.

15] 2-Pyrrolidine carboxylic acid (0.68 g, 5.92 mmol)
was added to a solution of 6-bromo-2-pyridine-

carboxaldehyde (1.0 g, 5.38 mmol) to give 1-(6-bromopyridin-2-ylmethyl)-pyrrolidine-2-carboxylic acid as a white solid. MS *m/z*: 285.1 (M+H). Calc'd for C₁₁H₁₃BrN₂O₂ - 285.14.

5

16] 3-Methylpiperidine (0.33 mL, 2.8 mmol) was added to a solution of 6-bromo-2-pyridine-carboxaldehyde (350 mg, 1.88 mmol) to give 2-bromo-6-[(3-methylpiperidyl)methyl]pyridine as a white solid. MS *m/z*: 269.1 (M+H). Calc'd for C₁₂H₁₇BrN₂ - 269.18.

10

Preparation O: 6-Morpholin-4-ylmethyl-pyridin-2-ylamine

15 NH₄OH (2 mL) and Cu powder (10 mg, 0.15 mmol) were added to a solution of 2-bromo-6-morpholinylpyridine (231 mg, 0.90 mmol) in iPrOH (5 mL) and the resulting mixture was heated at 100°C for 36 h in a sealed tube. After cooling to RT, the mixture was partitioned between H₂O and EtOAc. The 20 organic layer was collected, washed with brine, and dried over Na₂SO₄. Concentration *in vacuo* gave the tilted compound as a pale yellow solid. MS *m/z*: 194.1 (M+H).

25 The following amines were prepared from the corresponding bromo compounds (prepared by Preparation N) in a manner similar to that described in General Preparation O:

1] 1-(6-amino-pyridin-2-ylmethyl)-piperidine-4-carboxylic acid ethyl ester as brown liquid. MS 30 *m/z*: 264.2 (M+H). Calc'd for C₁₄H₂₁N₃O₂: 263.34.

2] 2-amino-6-[N'-*tert*-butoxycarbonyl-N'-2-(1-hydroxy-4-methyl)pentylamino]methylpyridine as a brown

liquid. MS m/z: 324.3 (M+H). Calc'd for C₁₇H₂₉N₃O₃: 323.2.

5 3] 2-amino-6-(4-ethoxyacetalpiperidinyl)-
methylpyridine as a white solid. MS m/z: 250
(M+2H). Calc'd for C₁₃H₁₉N₃O₂: 249.1.

10 4] 2-Amino-6-(3,5-dimethylpiperidinyl)methyl-pyridine
as a yellow solid. MS m/z: 220.3 (M+H). Calc'd for
C₁₃H₂₁N₃: 219.

15 5] 2-Amino-6-(4-methylpiperidinyl)methylpyridine as a
yellow solid. MS m/z: 206.3 (M+H). Calc'd for
C₁₂H₁₉N₃: 205.28.

6] 2-Amino-6-(2-methylpiperidinyl)methylpyridine as a
yellow liquid. MS m/z: 206.3 (M+H). Calc'd for
C₁₂H₁₉N₃: 205.28.

20 7] 2-Amino-6-[(4-(1-pyrrolidinyl)piperidinyl)methyl]-
pyridine as a brown liquid. MS m/z: 261.1 (M+2H).
Calc'd for C₁₂H₁₉N₃: 260.

25 8] 2-Amino-6-(3-hydroxypiperidinyl)methylpyridine as a
yellow liquid. MS m/z: 410.9 (M+H). Calc'd for
C₁₁H₁₇N₃O: 410.5.

9] 2-Amino-6-(azaperhydroepinylmethyl)pyridine as a
white solid. MS m/z: 206.1 (M+H). Calc'd for
C₁₂H₁₉N₃: 205.32.

30 10] 2-Amino-6-[(4-hydroxypiperidyl)methyl]pyridine as
a pale yellow oil. MS m/z: 208.1 (M+H). Calc'd
for C₁₁H₁₇N₃O - 207.27.

11] 2-Amino-6-[(*N*-*tert*-butoxycarbonyl-*N*-(3-hydroxypropyl)amino)methyl]pyridine as a pale yellow oil. MS *m/z*: 282.3 (M+H). Calc'd for C₁₄H₂₃N₃O₃ - 281.35.

5

12] Ethyl 1-[(6-aminopyridin-2-yl)methyl]-piperidine-3-carboxylate as a pale yellow oil. MS *m/z*: 264.1 (M+H). Calc'd for C₁₄H₂₁N₃O₂ - 263.34.

10

13] Ethyl 1-[(6-aminopyridin-2-yl)methyl]-piperidine-2-carboxylate as a pale yellow oil. MS *m/z*: 264.1 (M+H). Calc'd for C₁₄H₂₁N₃O₂ - 263.34.

15

14] *N,N*-Diethyl 1-(6-aminopyridin-2-ylmethyl)-piperidine-3-carboxamide as a pale yellow oil. MS *m/z*: 291.5 (M+H). Calc'd for C₁₆H₂₆N₄O - 290.40.

15] 1-(6-Aminopyridin-2-ylmethyl)-pyrrolidine-2-carboxylic acid as a white solid. MS *m/z*: 220.3 (M-H). Calc'd for C₁₁H₁₅N₃O₂ - 221.26.

20

16] 2-Amino-6-[(3-methylpiperidyl)methyl]pyridine as a pale yellow solid. MS *m/z*: 206.5 (M+H). Calc'd for C₁₂H₁₉N₃ - 205.30.

25

17] 1-(6-Aminopyridin-2-ylmethyl)-piperidine-3-carboxylic acid as a pale yellow oil. MS *m/z*: 235.0 (M+H). Calc'd for C₁₂H₁₇N₃O₂ - 235.28.

30

Preparation P: 4-(6-Aminopyridin-2-yloxy)-benzonitrile

To a stirred solution of 4-cyanophenol (1.7 g, 14.3 mmol) in 45 mL dry DMF was added NaH (0.71 g, 17.7 mmol).

After stirring at RT for 15 min, 2,6-dibromopyridine (3.2 g, 13.4 mmol) was added and the mixture was heated at 95°C for 24 h. After cooling to RT, 100 mL of H₂O was added and the mixture was extracted with EtOAc (2x100 mL). The combined 5 organic layers were washed with 40 mL brine, dried over MgSO₄ and concentrated in vacuo. The crude intermediate was dissolved in 20mL IpOH, transferred to a Teflon lined pressure vessel and 20 mL of conc. NH₄OH was added. Powdered Cu (1 g) was added and the vessel was sealed and 10 heated at 140°C for 24 h. After cooling to RT, the Cu was removed by filtration and the filtrate was diluted with 75 mL of H₂O and extracted with EtOAc (2x75 mL). The organic layers were washed with brine, dried over MgSO₄ and 15 concentrated in vacuo. The compound was purified by chromatography on silica gel using 10:1 CHCl₃/(~2M NH₃/MeOH) as eluent to afford the title compound as a dark oil. MS m/z: 212.2 (M+H).

The following compounds were prepared from 2,6-dibromopyridine in a manner similar to that described in 20 General Preparation P:

- 1] 6-Phenoxy-pyridin-2-ylamine: MS m/z: 187.2 (M+H).
Calc'd for C₁₁H₁₀N₂O: 186.08.
- 25 2] 6-(4-Methylphenoxy)pyridin-2-ylamine: MS m/z: 201.3 (M+H). Calc'd for C₁₂H₁₂N₂O: 200.09.
- 3] 6-(2,4-Dimethylphenoxy)pyridin-2-ylamine: MS m/z: 30 215.3 (M+H). Calc'd for C₁₃H₁₄N₂O: 214.11.
- 4] 6-[4-(1-Imidazolyl)phenoxy]pyridin-2-ylamine: MS m/z: 253.3 (M+H). Calc'd for C₁₄H₁₂N₄O: 252.10.

5] 6-[4-[1,3]Dioxolan-2-yl-phenoxy]pyridin-2-ylamine: MS
m/z: 259.3 (M+H). Calc'd for C₁₄H₁₄N₂O₃: 258.10.

6] 6-(4-Fluorophenoxy)pyridin-2-ylamine: MS m/z: 205.2
5 (M+H). Calc'd for C₁₁H₉FN₂O: 204.07.

7] 6-(4-Difluorophenoxy)pyridin-2-ylamine: MS m/z:
223.2 (M+H). Calc'd for C₁₁H₈F₂N₂O: 222.06.

10 8] tert-Butyl {2-[4-(6-aminopyridin-2-
yloxy)phenyl]ethyl}carbamate: MS m/z: 330.4 (M+H).
Calc'd for C₁₈H₂₃N₃O₃: 329.17.

9] 6-(2-Dimethylaminoethoxy)pyridin-2-ylamine: MS m/z:
15 182.2 (M+H). Calc'd for C₉H₁₅N₃O: 181.12.

10] 6-[(1-Methylpyrrolidin-2-yl)methoxy]pyridin-2-ylamine:
MS m/z: 208.3 (M+H). Calc'd for C₁₁H₁₇N₃O: 207.14.

20 11] 6-(1-Aza-bicyclo[2.2.2]oct-3-yloxy)pyridin-2-ylamine:
MS m/z: 220.3 (M+H). Calc'd for C₁₂H₁₇N₃O: 219.14.

12] tert-Butyl 3-[(6-aminopyridin-2-yl)oxymethyl]-
25 azetidine-1-carboxylate: MS m/z: 280 (M+H). Calc'd
for C₁₄H₂₁N₃O₃: 279.16.

13] tert-Butyl 4-[2-(6-Aminopyridin-2-yloxy)ethyl]-
piperidine-1-carboxylate: MS m/z: 322 (M+H). Calc'd
for C₁₇H₂₇N₃O₃: 321.21.

30 Preparation Q: 2-Bromo-6-[N'-tert-butoxycarbonyl-N'-2-(1-
hydroxy-4-methyl)pentylamino]methylpyridine
To 2-bromo-6-[2-N-(1-hydroxy-4-methyl)-
pentylamino]methylpyridine (550 mg, 1.91 mmol) in dry CH₂Cl₂,

(10 mL) was added (Boc)₂O (460 mg, 2.106 mmol). The resulting mixture was stirred under N₂ at RT for 15 h. The solvent was removed and the residue was extracted with CHCl₃. The organic layer was wash with H₂O, brine, and 5 dried over MgSO₄ and removed to give a yellow liquid. MS m/z: 387.6 (M+H). Calc'd for C₁₇H₂₇BrN₂O₃: 387.32.

The following BOC protected compounds were prepared from the corresponding amines (prepared by Preparation N) in 10 a manner similar to that described in General Preparation Q:

1] 2-Bromo-6-[(N-*tert*-butoxycarbonyl-N-(3-hydroxypropyl)amino)methyl]pyridine was prepared from 2-bromo-6-[(3-hydroxypropyl)-amino]-15 methylpyridine (300 mg, 1.22 mmol) [purified by chromatography on silica gel (hexane/acetone, 80/20)] as a colorless oil. MS m/z: 345.1 (M+H). Calc'd for C₁₄H₂₁BrN₂O₃ - 345.23.

20 **Preparation R: 2,2-Dimethyl-N-[6-(2-methylimidazol-1-ylmethyl)pyridin-2-yl]propionamide**

A solution of 2-methylimidazole (68 mg, 0.83 mmol) in dry THF (8 mL) was treated under N₂ with NaH (33 mg, 0.83 mmol, 60% in mineral oil) at 0°C. After the addition, the 25 mixture was warmed to RT and stirred for 0.5 h. It was then treated dropwise with a solution of *N*-pivaloyl-2-amino-6-bromomethylpyridine (150 mg, 0.55 mmol; M.V. Papadopoulou, et al., *J. Heterocyclic Chem.*, 1995, 32, 675-681) in dry THF (10 mL) over period of 15 min. After the addition, it was 30 stirred for 1 h. The resulting mixture was quenched with saturated NH₄Cl (3 mL). Solvent was removed and the residue was extracted with CHCl₃. The organic layer was washed with H₂O, brine, dried over MgSO₄, and concentrated in vacuo to

yield the title compound as light brownish solid. MS *m/z*: 272.2 (M+H). Calc'd. for C₁₆H₂₁N₃O - 271.37.

5 The following amines were prepared from the corresponding bromomethylpyridine in a manner similar to that described in Preparation R:

10 1] 2,2-Dimethyl-N-[6-(4-(N,N-dimethylamino-methyl)phenyloxymethyl)pyridin-2-yl]propionamide.
MS *m/z*: 342 (M+H).

Preparation S: N-(6-Azidomethylpyridin-2-yl)-2,2-dimethylpropionamide

15 *N*-Pivaloyl-2-amino-6-bromomethylpyridine (1.1 g, 4.05 mmol; M.V. Papadopoulou, et al., *J. Heterocyclic Chem.*, 1995, 32, 675-681) was dissolved in dry THF (15 mL). NaN₃ (530 mg, 8.1 mmol) and dry DMF (5 mL) was added and the resulting mixture was heated to reflux under N₂ for 2 h. After cooling to RT, solvent was removed and the residue was 20 partitioned between H₂O and CHCl₃. The organic layer was washed with H₂O, brine, dried over MgSO₄, and concentrated *in vacuo* to give the title compound as a pale yellow solid. MS *m/z*: 234.1 (M+H). Calc'd. for C₁₁H₁₅N₅O - 233.28.

25 **Preparation T: 6-Azidomethyl-pyridin-2-ylamine**

2-(N'-Pivaloyl)amino-6-azidomethylpyridine (680 mg, 2.91 mmol) was dissolved in MeOH (20 mL) and KOH was added (3.4 g, 60.6 mmol). The resulting mixture was heated to reflux under N₂ for 2 h. After cooling to RT, pH was 30 adjusted to 7 followed by removing the solvent. The residue was partitioned between H₂O and CHCl₃, and the aqueous layer was extracted more with CHCl₃. The combined organic layers was washed with H₂O, brine, dried over MgSO₄, and

concentrated in vacuo to yield the title compound as brown solid. MS m/z : 150.3 (M+H). Calc'd. for $C_6H_7N_5$: 149.15.

5 The following amines were prepared from the corresponding bromo compounds (prepared by Preparations R-S, and AA) in a manner similar to that described in Preparation T:

10 1] 3-(2-Methylimidazol-1-ylmethyl)phenylamine. MS
 m/z : 189.3 (M+H). Calc'd. for $C_{10}H_{12}N_4$ - 188.23.

15 2] 2-Amino-6-[4-(dimethylamino)methyl]phenoxyethyl-pyridine. MS m/z : 258 (M+H).

20 3] 2-Amino-6-[1-(*N*-tert-butoxycarbonyl)amino]-ethoxymethyl-pyridine. MS m/z : 268 (M+H).

4] 2-Amino-6-[4-(methylphenyl)oxymethyl]pyridine. MS
 m/z : 215 (M+H).

25 5] 2-Amino-6-[1-(*N*-tert-butoxycarbonyl)amino]-ethoxymethyl-pyridine. MS m/z : 267 (M+H)

6] 2-Amino-5-[1-morpholinylmethyl]pyridine. MS m/z : 194 (M+H).

7] 5-Methoxymethyl-pyridin-2-ylamine.

30 Preparation U: Methyl 1-(6-aminopyridin-2-ylmethyl)-pyrrolidine-2-carboxylate

Concentrated H_2SO_4 (1.0 mL) was added to a solution of 1-(6-aminopyridin-2-ylmethyl)-pyrrolidine-2-carboxylic acid (620 mg, 2.80 mmol) in MeOH (15 mL) and the resulting mixture was heated at 80°C for 10 h. After cooling to RT,

the mixture was quenched with saturated 2 M Na_2CO_3 solution and concentrated *in vacuo*. CHCl_3 (15 mL) was added and the solution washed with 1.0 N NaOH solution (15 mL). The organics were collected and the aqueous layer was extracted 5 with $\text{CHCl}_3/\text{IpOH}$ (3/1, 3x10 mL). The combined organics were dried over MgSO_4 and concentrated *in vacuo*. The crude compound was purified by chromatography on silica gel ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 95/5) to give a pale yellow oil. MS *m/z*: 236.1 ($\text{M}+\text{H}$). Calc'd for $\text{C}_{12}\text{H}_{17}\text{N}_3\text{O}_2$ -235.28.

10

Preparation V: 3-Methyl-2-(phthalimidyl)pyridine

2-Amino-3-picoline (1.00 mL, 8.62 mmol) was dissolved in DMF (30 mL) at 23°C, and treated with solid carboethoxy-phthalimide (1.89 g, 8.64 mmol), followed by TEA (1.44 mL, 15 10.3 mmol). The resulting solution was stirred at 23°C for 15 h. After 15 h, the mixture was diluted with EtOAc (50 mL), and washed with saturated NaCl (1X50 mL), H_2O (1X50 mL), dried (MgSO_4), and concentrated *in vacuo* to a yellow solid. Purification over silica gel (0 to 50% 20 EtOAc/Hexanes) provided the title compound as a white solid.

Preparation W: 3-(Dibromomethyl)-2-(phthalimidyl)pyridine

3-Methyl-2-(phthalimidyl)pyridine (360 mg, 1.51 mmol) was dissolved in CCl_4 (5 mL), and treated with NBS (267 mg, 25 1.50 mmol), followed by AIBN (46.9 mg, 0.29 mmol). The resulting suspension was warmed to reflux for 2 h, treated again with AIBN (55.4 mg, 0.34 mmol), and heated at reflux an additional 12 h. After 12 h, AIBN was again added (96.7 mg, 0.59 mmol) and reflux was continued. After 2 h, more 30 AIBN was added (59.6 mg, 0.36 mmol), and reflux continued. After 2h, additional NBS was added (253 mg, 1.42 mmol) and the mixture was treated with additional AIBN (49.6 mg, 0.30 mmol), and heated at reflux an additional 12 h. The mixture was cooled to RT, diluted with EtOAc (50 mL), washed with

saturated NaCl (1X50 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. The resulting white solid was purified over silica gel (0 to 40% EtOAc/Hexanes) to provide the title compound. MS *m/z*: 397 (M+H).

5

Preparation X: 2-(phthalimidyl)-3-(1-piperidinylmethyl)-pyridine

3-(Dibromomethyl)-2-(phthalimidyl)pyridine (185 mg, 0.47 mmol) was dissolved in CH_2Cl_2 (2 mL) and treated with 10 piperidine (.460 mL, 4.66 mmol), and glacial AcOH (.160 mL, 2.80 mmol) in a dropwise fashion. The resulting yellow solution was stirred at 23°C for 2 h, then treated with solid $NaBH(OAc)_3$ (393 mg, 1.86 mmol) in one portion, and stirring was continued for 14 h. After stirring 14 h at 15 23°C, the mixture was treated with 2M K_2CO_3 (6 mL), and stirred for 1 h. After 1 h, the mixture was diluted with EtOAc (50 mL) and washed with H_2O (1X50 mL), and saturated 20 $NaCl$ (1X50 mL). The organic phase was then dried ($MgSO_4$) and concentrated *in vacuo* to provide the title compound as a yellow residue. The crude material was used in subsequent transformations without further purification. MS *m/z*: 323 (M+H).

Preparation Y: 2-Amino-3-(1-piperidinylmethyl)-pyridine

25 2-(Phthalimidyl)-3-(1-piperidinylmethyl)-pyridine (196 mg, 0.609 mmol) was dissolved in EtOH (95%, 2 mL) at 23°C, and treated with hydrazine monohydrate (0.0320 mL, 0.670 mmol) in a dropwise fashion. The resulting mixture was warmed to reflux and stirred for 3 h at reflux. The 30 solution was treated with additional hydrazine monohydrate (0.150 mL, 3.050 mmol), and reflux continued. After 14 h at reflux, the mixture was cooled to RT, and concentrated using a rotary evaporator to a white paste. The resulting white paste was dissolved in $CHCl_3:IpOH$ (3:1, 75 mL), and washed

with saturated NaHCO_3 (3X50 mL), and H_2O (1X50 mL). The organic layer was dried over MgSO_4 and concentrated in vacuo to provide the title compound as a white solid. MS m/z : 192 (M+H).

5

Preparation Z: N-Pivaloyl 2-amino-5-(bromomethyl) pyridine

N -Pivaloyl-2-amino-5-methylpyridine (5.12 g, 26.6 mmol) was dissolved in CCl_4 (75 mL) at 23°C, and treated with NBS (9.69 g, 54.4 mmol), followed by AIBN (937 mg, 5.71 mmol) with stirring. The resulting orange, biphasic suspension was then warmed to reflux for 4 h. After 4 h at reflux, the rust-colored mixture was cooled to RT, filtered through a Celite® pad, and concentrated in vacuo to a red residue. Purification over silica gel (gradient, 0 to 25% EtOAc/hexanes) provided the title compound as a light yellow solid. MS m/z : 272 (M+H).

Preparation AA: N-Pivaloyl-2-amino-5-[2-(*N*-tert-butoxycarbonyl)amino]ethoxymethylpyridine

N -Pivaloyl-2-amino-5-bromomethylpyridine (484 mg, 1.78 mmol) was dissolved in THF (6 mL) at 23°C, and treated with 2-(*N*-tert-butoxycarbonyl)aminoethanol (0.551 mL, 3.56 mmol), followed by NaH (60% suspension in mineral oil, 221 mg, 5.52 mmol) with stirring. The resulting mixture was stirred at 23°C for 14 h, then treated with additional NaH (75.6 mg, 1.89 mmol) as well as DMSO (1 mL), and stirred an additional 5 h at 23°C. After 5 h at 23°C, the solution was warmed to 55°C for 3 h, then cooled to RT. The mixture was treated with saturated NaHCO_3 (10 mL), diluted with EtOAc (50 mL), and washed with saturated NaHCO_3 (2X50 mL). The mixture was dried over MgSO_4 and purified over silica gel to provide the title compound as a pale yellow oil. MS m/z : 352 (M+H).

The following amines were prepared from the corresponding bromomethylpyridine in a manner similar to that described in General Preparation AA:

5 1] 2,2-Dimethyl-N-[6-(N-(tert-butoxycarbonyl)-amino-1-ethoxymethyl)pyridin-2-yl]propionamide. MS *m/z*: 352 (M+H).

10 2] *N*-Pivaloyl-2-amino-6-[(4-methylphenyl)-oxymethyl]-pyridine. MS *m/z*: 299 (M+H).

15 3] *N*-Pivaloyl-2-amino-5-[(4-methylphenyl)-oxymethyl]pyridine. MS *m/z*: 299 (M+H).

15 Preparation AB: *N*-Pivaloyl-2-amino-5-[1-morpholinylmethyl]pyridine

N-Pivaloyl-2-amino-5-bromomethylpyridine (478 mg, 1.76 mmol) was dissolved in THF at 23°C with stirring and treated with morpholine (0.770 mL, 8.81 mmol) in a dropwise fashion.

20 The resulting brown mixture was stirred at 23°C for 14 h. After stirring 14 h, the mixture was treated with saturated NaHCO₃ (2 mL) and stirred an additional 5 h at 23°C. After 5 h, the brown mixture was warmed to 55°C for 3 h, then cooled to RT and diluted with EtOAc (50 mL). The mixture 25 was washed with saturated NaHCO₃ (2X50 mL), dried (MgSO₄), and concentrated to a brown residue which was immediately purified over silica gel (0 to 5% MeOH/CHCl₃) to provide the title compound as a yellow oil. MS *m/z*: 278 (M+H).

30 Preparation AC: 2-(Butyloxycarbonyl)amino-6-methylpyridine

To a 2-L 3-neck Miller flask charged with 2-amino-6-methylpicoline (15 g, 138.7 mmol) and dry THF (1 L) was added di-tert-butyl dicarbonate (33.3 g, 152.6 mmol) then TEA (21.2 mL, 152.6 mmol) via addition funnel at 0°C. The

reaction mixture was warmed to RT and added DMAP (1.7 g, 13.9 mmol). After 3.5 h, extracted with EtOAc, washed with saturated NH₄Cl, H₂O (3x), and brine (3x), dried (MgSO₄) and concentrated in vacuo to afford the crude material as a 5 turbid yellow oil. Trituration with hexane formed a precipitate which was filtered and the filtrate was concentrated in vacuo to give the title compound as a yellow oil.

10 **Preparation AD: 6-Bromomethyl-2-(butyloxycarbonyl)amino-pyridine**

To a solution of N-Boc-2-amino-6-picoline (28.7 g, 138 mmol) and CCl₄ (500 mL) was added NBS (27.1 g, 151.8 mmol) and AIBN (2.3 g, 13.8 mmol) and heated to reflux. After 2 15 h, added 0.1 equivalent of AIBN. The reaction mixture was heated at reflux for 20 h, filtered and concentrated in vacuo to give a dark oil. Purified by silica flash chromatography (100% hexane to 5% EtOAc/Hexane) to afford the desired as a yellow oil. MS m/z: 288.0 (M+H)

20

Preparation AE: 2-(Butyloxycarbonyl)amino-6-cyanomethylpyridine

To a solution of N-Boc-2-amino-6-methylbromidepyridine (12 g, 41.8 mmol) and EtOH (250 mL) was added NaCN (2 g, 25 41.8 mmol). The reaction mixture was heated to reflux for 2 h then cooled to RT and concentrated in vacuo. Purification by silica flash chromatography (100% Hexane to 20% EtOAc/Hexane) afforded the title compound as a yellow oil. MS m/z: 234.0 (M+H).

30

Preparation AF: 2-Amino-6-cyanomethylpyridine

To a solution of N-Boc-2-amino-6-methylnitrilepyridine and CH₂Cl₂ (10 mL) was added TFA (8 mL) and stirred at RT. After 3 h, the mixture was concentrated in vacuo, diluted

with EtOAc and saturated NaHCO₃ was carefully added. The mixture was washed with saturated NaHCO₃ (2x) and brine, dried (MgSO₄) and concentrated in vacuo to afford the title compound as a yellow solid.

5

Preparation AG: 6-Aminoethyl-2-(butyloxycarbonyl)amino-pyridine

A solution of N-Boc-2-amino-6-methylnitrile-pyridine (1 g, 4.3 mmol) and EtOH (25 mL) was hydrogenated over 20% Pd(OH)₂/C at RT and 40 psi. After 18 h, the mixture was filtered through Celite® and eluted with EtOAc. The filtrate was concentrated in vacuo to afford the title compound as a white foamy solid.

15 **Preparation AH: 2-Amino-6-(phthalimidyl)ethyl-pyridine**

To a solution of N-Boc-2-amino-6-ethylaminopyridine (1 g, 4.3 mmol) and CHCl₃ (25 mL) was added phthalic anhydride (0.64 g, 4.3 mmol). Heated to 70°C for 15 h then at RT for 5 days. The mixture was washed with H₂O and brine, dried (MgSO₄) and concentrated in vacuo to give crude N-Boc-2-amino-6-ethylphthalimidylpyridine, which was used without further purification. To a solution of crude N-Boc-2-amino-6-ethylphthalimidylpyridine (1.6 g, 4.3 mmol) and CH₂Cl₂ (10 mL) was added 10 mL of TFA and the mixture was stirred at RT. After 30 min, the mixture was concentrated in vacuo. The residue was diluted with 90% MeOH/CH₂Cl₂ and treated with solid NaHCO₃, stirred for 15 min then filtered. The filtrate was concentrated in vacuo to afford the title compound as a yellow solid. MS m/z: 268.2 (M+H).

30

Preparation AI: 2-[(6-Bromopyridin-2-yl)methylamino]-propan-1-ol

To a stirred solution of the (6-bromo-2-pyridyl)-formaldehyde (0.52 g, 2.8 mmol) in toluene (14 mL) was added

DL-2-amino-1-propanol (0.67 mL). The resulting mixture was heated to reflux with a Dean-Stark trap for 3 h under N₂ until complete formation of the imine was observed. The mixture was brought to RT followed by the addition of a 5 solution of NaBH(OAc)₃ (2.0 g, 9.8 mmol) in AcOH (6 mL). The resulting mixture was stirred at RT and under N₂ for 56 h. The mixture was neutralized (pH 7.0) with a saturated solution of NaHCO₃ (aq) and extracted with CH₂Cl₂ (3x50mL). The aqueous layer was concentrated by rotary evaporation and 10 the residue obtained was extracted with CH₂Cl₂ (3x50mL). The organic layers were combined, dried over MgSO₄, filtered and concentrated by rotary evaporation to afford the title compound as a pale yellow oil. EI-MS m/z 245 (M+H).

15 **Preparation AJ: (tert-Butoxy)-N-[(6-bromo(2-pyridyl)methyl]-N-(2-hydroxy-isopropyl)carboxamide**

To a stirred solution of 2-[(6-bromo-2-pyridyl)-methyl]aminopropan-1-ol (0.55 g, 2.2 mmol) in dry CH₂Cl₂ (11 mL) was added Boc₂O (0.51 g, 2.42 mmol). The resulting 20 mixture was stirred at RT and under N₂ for 15 h. The mixture was concentrated by rotary evaporation and purified on silica gel (2:1 hexanes/EtOAc, 5:95 MeOH/CH₂Cl₂ and, 10:90 MeOH/CH₂Cl₂) as eluent to afford the title compound as an off-white oil. EI-MS m/z 345 (M+H).

25

Preparation AK: (tert-Butoxy-N-[(6-bromo(2-pyridyl))-methyl]-N-(1-methyl-2-oxoethyl)carboxamide

To a dry flask was added oxalyl chloride (72 μ L) followed by the addition of dry CH₂Cl₂ (2 mL). The resulting 30 colorless solution was brought to -63°C (dry ice/CHCl₃) and a solution of DMSO (80 μ L) in 0.5 mL dry CH₂Cl₂ was slowly added dropwise. A solution of (tert-butoxy)-N-[(6-bromo(2-pyridyl)methyl]-N-(2-hydroxy-isopropyl)carboxamide (0.19 g, 0.55 mmol) in dry CH₂Cl₂ (2 mL), was added slowly drop wise.

The resulting mixture was kept at -63°C and stirred for 30 min, followed by the slow addition of a solution of TEA (0.31 mL) in dry CH₂Cl₂ (1 mL). The mixture was stirred at -63°C until all the starting material was consumed (checked by MS). The mixture was brought to -20°C, quenched with a saturated solution of NH₄Cl (aq) and diluted with EtOAc. The organic phase was separated and the aqueous phase was extracted with EtOAc (3x20mL). The organic layers were combined, dried over MgSO₄, filtered and concentrated by rotary evaporation to afford the title compound as a pale yellow semi-solid. EI-MS m/z 343 (M+H).

Preparation AL: N-[2-(diethylamino)-isopropyl](tert-butoxy)-N-[(6-bromo(2-pyridyl)methyl]-carboxamide

To a stirred solution of (tert-butoxy-N-[(6-bromo(2-pyridyl)methyl]-N-(1-methyl-2-oxoethyl)-carboxamide (0.15 g, 0.44 mmol) in toluene (3 mL) was added DEA (0.2 mL). The resulting mixture was heated to reflux in a Dean-Stark trap under N₂ for 3 h. The mixture was brought to RT followed by the addition of a solution of NaBH(OAc)₃ (0.33 g, 1.54 mmol) in AcOH (6 mL). The yellow-solution was stirred at RT and under N₂ for 15 h. The mixture was diluted with EtOAc (20 mL) and washed with a saturated solution of NaHCO₃ (aq) (50 mL). The organic phase was separated, dried (MgSO₄), filtered and concentrated by rotary evaporator to afford the title compound as a brown/yellow oil. EI-MS m/z 400 (M+H).

Preparation AM: N-[2-(diethylamino)isopropyl](tert-butoxy)-N-[(6-amino(2-pyridyl)methyl]-carboxamide

To a stirred solution of N-[2-(diethylamino)-isopropyl](tert-butoxy)-N-[(6-bromo(2-pyridyl)methyl]-carboxamide (80 mg 0.2 mmol) in IpOH (4 mL) in a sealed tube, was added NH₄OH (28-30%, 6 mL) followed by an excess of Cu. The resulting solution was heated under pressure at

90°C for 24 h. The mixture was brought to RT, diluted with H₂O (20 mL) and extracted with CHCl₃ (3x20mL). The organic layers were combined, dried over MgSO₄, filtered and concentrated by rotary evaporation to afford the title 5 compound as a pale-yellow oil. EI-MS m/z 337 (M+H).

Preparation AN: Methyl 2-[(6-bromo-2-pyridylmethyl)amino]-3-methyl-butyrate

To a stirred solution of L-valine methyl ester 10 hydrochloride (0.54 g, 3.24 mmol) in dry toluene (15 mL) at 80°C was added DIEA (2.0 mL 11 mmol) followed by (6-bromo-2-pyridyl)formaldehyde (0.50 g, 2.70 mmol). The resulting mixture was heated at 80°C for 3 h. The reaction was brought to RT and a solution of NaBH(OAc)₃ (1.4 g, 6.75 mmol) in 15 glacial AcOH (4 mL) was added. The resulting mixture was stirred for 15 h and concentrated by rotary evaporation. The resulting yellow oil was dissolved in CH₂Cl₂ (100 mL), washed with a saturated solution of NaHCO₃ (aq) (50 mL), brine (50 mL), dried over Na₂SO₄, filtered, concentrated by 20 rotary evaporation and purified by flash chromatography (2:1 hexanes/EtOAc) to afford the title compound as a pale-yellow oil. EI-MS m/z 301 (M+H).

Preparation AO: 2-[(6-Bromo-2-pyridylmethyl)amino]-3-methyl-butanol

To a stirred solution of (tert-butoxy)-N-[(6-bromo(2-pyridyl)methyl)-N-[2-oxomethoxide-1-(methylethyl)-ethyl]carboxamide (0.47 g, 1.57 mmol) in dry toluene (25 mL) at -78°C was added dropwise DIBAL-H (1.0 M solution in 30 hexane, 4.7 mL). The resulting brown-solution was stirred at -78°C for 3 h, brought to RT and stirred until starting material was consumed. The organic layer was separated, dried over Na₂SO₄, filtered, concentrated by rotary evaporation and purified on silica gel (10:90 MeOH/CH₂Cl₂)

to afford the title compound as a yellow oil. EI-MS m/z 273 (M+H).

Preparation AP: tert Butyl (6-bromopyridin-2-ylmethyl)-(1-hydroxymethyl-2-methyl-propyl)-carbamate

5 To a stirred solution of 2-[(6-bromo-2-pyridylmethyl)amino]-3-methyl-butanol (0.30 g, 1.10 mmol) in CH₂Cl₂ (5 mL) was added Boc₂O (0.26 g, 1.21 mmol). The resulting solution was stirred for 15 h, concentrated by 10 rotary evaporation and purified on silica gel (5:95 MeOH/CH₂Cl₂ and 10:90 MeOH/CH₂Cl₂) to afford the title compound as a pale yellow solid. EI-MS m/z 373 (M+H).

Preparation AQ: tert Butyl (6-bromopyridin-2-ylmethyl)-(1-formyl-2-methyl-propyl) carbamate

15 To a flame-dried flask was added oxalyl chloride (70 μ L) followed by the addition of dry CH₂Cl₂ (2 mL). The resulting colorless solution was brought to -63 °C (dry ice/CHCl₃) and a solution of DMSO (70 μ L) in 0.5 mL dry CH₂Cl₂ was slowly added drop wise. The (tert-butoxy)-N-[(6-bromo(2-pyridyl)methyl)-N-[2-hydroxy-1-(methylethyl)ethyl]carboxamide (0.19 g, 0.51 mmol), previously dissolved in dry CH₂Cl₂ (2 mL), was added slowly dropwise. The resulting mixture was kept at -63°C and 20 stirred for 30 min followed by the slowly addition of a solution of TEA (0.3 mL) in dry CH₂Cl₂ (1 mL). The mixture was stirred at -63°C until all the starting material was consumed (checked by MS) (1.5 h). The mixture was brought to -20°C, quenched with a saturated solution of NH₄Cl (15 mL) 25 and diluted with EtOAc (35 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (3x30mL). The organic layers were combined, dried over MgSO₄, filtered and concentrated by rotary evaporation 30

without further purification to afford the title compound as a yellow-semi solid. EI-MS m/z 371 (M+H).

Preparation AR: tert-Butyl (6-bromopyridin-2-ylmethyl)-(1-diethylaminomethyl-2-methyl-propyl)carbamate

5 To a stirred solution of (tert-butoxy)-N-[(6-bromo(2-pyridyl)methyl)-N-[1-(methylethyl)-2-oxoethyl]carboxamide (0.17 g, 0.46 mmol) in toluene (5 mL) was added DEA (0.14 mL). The resulting mixture was heated to reflux in a Dean-
10 Stark trap under N₂ for 3 h. The mixture was brought to RT followed by the addition of a solution of NaBH(OAc)₃ (0.34 g, 1.61 mmol) in glacial AcOH (6 mL). The yellow-solution was stirred at RT and under N₂ for 15 h. The mixture was diluted with EtOAc (20 mL) and washed with a saturated
15 solution of NaHCO₃ (aq) (15 mL). The aqueous layer was separated and concentrated under reduced pressure. The solid obtained was extracted with CH₂Cl₂. The extracts were combined, dried over MgSO₄, filtered and, concentrated by rotary evaporation to afford the title compound as a pale
20 yellow oil. EI-MS m/z 428 (M+H).

Preparation AS: tert-Butyl (6-aminopyridin-2-ylmethyl)-(1-diethylaminomethyl-2-methyl-propyl)carbamate

25 To a stirred solution of N-[1-[(diethylamino)-methyl]-2-methylpropyl](tert-butoxy)-N-[(6-bromo(2-pyridyl)methyl]carboxamide (5 mg, 0.012 mmol) in iPrOH (5 mL) in a sealed tube, was added NH₄OH (28-30% 6 mL) followed by excess Cu. The resulting solution was heated under pressure at 90°C for 24 h. The mixture was brought to RT, 30 diluted with H₂O (10 mL) and extracted with CHCl₃ (3x20mL). The organic layers were combined, dried over MgSO₄, filtered and concentrated by rotary evaporation to afford the title compound as a green oil. No purification was required. EI-MS m/z 365 (M+H).

Preparation AT: 2-Bromo-6-(piperidin-1-ylmethyl)pyridine

To a stirred solution of 6-bromo-2-pyridine carboxaldehyde (5.05 g, 27 mmol) in anhydrous CH₂Cl₂ (200 mL) at RT, under N₂, piperidine (2.95 mL, 29 mmol) was added, followed by NaBH(OAc)₃ (11.51 g, 54 mmol) and AcOH (6.2 mL, 108 mmol) 30 min later. After 20 h, a 2M solution of Na₂CO₃(aq) (20 mL) was added. The mixture was vigorously stirred for an additional 30 min, washed successively with a saturated solution of NaHCO₃(aq) until the pH of the aqueous layer reached 7 (2x100mL), H₂O (100 mL) and brine (100 mL). The organic layer was separated, dried over MgSO₄, filtered and concentrated under reduced pressure to yield the title compound as a yellow oil. This was used crude in the next step. MS m/z: 255 (M+H), 257 (M+3).

Preparation AU: 2-Amino-6-(piperidin-1-ylmethyl)pyridine

To a solution of 2-bromo-6-(piperidylmethyl)pyridine (5.21 g, 20 mmol) in IpOH (30 mL) in a sealed tube at RT, a catalytic amount of Cu (100 mg) and 28-30% NH₄OH (35 mL) were added. The stirred suspension was heated to 95°C for 40 h. After cooling to RT, the reaction mixture was diluted with H₂O (100 mL) and extracted with EtOAc (4x80mL). The organic layers were combined, then washed with H₂O (50 mL) followed by brine (50 mL). The organic layer was separated, dried over Na₂SO₄, filtered and concentrated under reduced pressure to yield the title compound as a dark yellow oil. This was used as crude. MS m/z: 193 (M+H)+.

Preparation AV: Ethyl 2-(4-aminosulfonylphenyl) thiazole-4-carboxylate

In an oven-dried, 100-mL, round-bottomed flask were placed 4-cyanobenzenesulphonamide (4.1 g, 22.50 mmol), TEA (5 mL) in pyridine (40 mL). H₂S was bubbled through this

mixture for 1 h at RT. The reaction was diluted with EtOAc (125 mL) and H₂O (50 mL). The phases were separated, and the organic layer was washed with H₂O (4x25 mL) and brine (15 mL), dried over MgSO₄, and concentrated in vacuo to afford the crude thiobenzamide as an oily solid; MS m/z: 217 (M+H). In an oven-dried, 100-mL, round-bottomed flask were placed the crude thiobenzamide, ethyl bromopyruvate (3.0 mL, 23.66 mmol) in EtOH (40 mL). The reaction was heated to 75°C for 12 h, then cooled to RT. The mixture was concentrated in vacuo to give the crude sulfonamide as a yellow solid which was filtered, washed with H₂O (1x10 mL) and Et₂O (4x10 mL) to afford the title compound as a yellow solid. MS m/z: 313 (M+H).

15 Preparation AW: 2-(4-Aminosulfonylphenyl)thiazole-4-carboxylic acid

In an oven-dried, 100-mL, round-bottomed flask was placed ethyl 2-(4-aminosulfonylphenyl)thiazole-4-carboxylate (1300 mg, 4.2 mmol), LiOH monohydrate (350 mg, 8.3 mmol) in MeOH (40 mL) and H₂O (4 mL). The solution was heated to 75°C for 3 h, cooled to RT, and concentrated. The resulted yellow solid was dissolved in H₂O (10 mL), extracted with EtOAc (1x15 mL). The aqueous layer was acidified with 2N aqueous HCl (4.15 mL). The precipitate was filtered, and washed with H₂O (10 mL) to afford the title compound as a light-yellow solid. MS m/z: 285 (M+H).

Preparation AX: 2-(4-(4-morpholinyl)sulfonylphenyl)-thiazole-4-carboxylic acid

30 In a manner similar to that described for the preparation of 2-(4-aminosulfonylphenyl)thiazole-4-carboxylic acid, 460 mg of 4-(morpholinosulfonyl)-benzonitrile was treated with H₂S, ethyl bromopyruvate, and

LiOH successively to give the title compound. MS m/z: 355 (M+H).

5 **Preparation AY: 2-(4-Boc-aminophenyl)-thiazole-4-carboxylic acid**

In a manner similar to that described for the preparation of 2-(4-aminosulfonylphenyl)thiazole-4-carboxylic acid, 4-[(1,1-dimethylethoxy)carbonyl]-aminobenzonitrile was treated with H₂S, ethyl bromopyruvate, 10 and LiOH successively to give the title compound. MS m/z: 321 (M+H).

Preparation AZ: Ethyl 2-(phenoxy)thiazole-4-carboxylate

A mixture of the bromothiazole (1.03 g, 4.36 mmol) and 15 phenol (10.0 g, 106 mmol) was stirred at 180°C for 1 h, cooled to RT, diluted with 100 mL of EtOAc, washed with 1N NaOH (40x3), H₂O, and brine, then dried over MgSO₄, and concentrated *in vacuo* to yield a light yellow residue. Purification over silica gel (gradient, 5% to 10% 20 EtOAc/hexanes) provided the title compound. MS m/z: 250 (M+H)⁺.

Preparation BA: 2-(Phenoxy)thiazol-4-ylcarbonylazide

TEA (0.17 mL, 1.20 mmol) was added to a solution of 25 the thiazole carboxylic acid (0.13 g, 0.59 mmol) in 10 mL of THF at 0 °C. The mixture was stirred at 0°C for 20 min whereupon ethyl chloroformate (0.065 mL, 0.65 mmol) was added. After the mixture was stirred for 30 min, a solution of NaN₃ (0.043 g, 0.65 mmol) in 3 mL of H₂O was added, the 30 reaction was stirred for 30 min, then warmed to RT, diluted with 25 mL of H₂O, and extracted with EtOAc. The combined organic portions were washed with brine, dried over MgSO₄, filtered, and removal of the solvents in *vacuo* yielded the

title compound as a light brownish solid. MS *m/z*: 247 (M+H).

Preparation BB: 6-Chloro-thionicotinamide

5 To a solution of the 4-chloronicotinamide (5 g, 31.9 mmol) and dry THF (200 mL) was added P₂S₅ (15.6 g, 35.1 mmol) and Na₂CO₃ (3.7 g, 35.1 mmol). The mixture was heated at reflux for 1.5 h, cooled and filtered off a yellow solid. The filtrate was extracted with EtOAc, washed with H₂O and 10 brine; dried (MgSO₄) then concentrated *in vacuo* to give the title compound as a yellow solid. MS *m/z*: 173.0 (M+H).

Preparation BC: Ethyl 2-(6-chloro-3-pyridyl)thiazole-4-carboxylate

15 To a mixture of the 4-chloro-thionicotinamide (5.5 g, 31.9 mmol) and EtOH (300 mL) was added bromo-ethyl-pyruvate (4.4 mL, 35.1 mmol). The mixture was heated at reflux for 15 h, cooled and concentrated *in vacuo* to afford a yellow solid/orange oil. The oil was diluted with EtOAc and 20 filtered off yellow solid. The filtrate was filtered through Celite® and concentrated *in vacuo* to give a dark yellow oil. The oil was diluted with 2% MeOH/CH₂Cl₂ and filtered through a pad of silica gel (150 mL). Elution with 2% MeOH/CH₂Cl₂ (500 mL), followed by concentration *in vacuo* 25 afforded the title compound as a yellow crystalline solid. MS *m/z*: 269.1 (M+H).

Preparation BD: 2-(6-Methoxy-3-pyridyl)thiazole-4-carboxylic acid

30 To a solution of the ethyl 2-(6-chloro-3-pyridyl)thiazole-4-carboxylate (0.61 g, 2.3 mmol) and MeOH (50 mL) was added solid NaOMe (135 mg, 2.5 mmol) and stirred at RT. After 3 h the ethyl ester transesterified to the methyl ester. NaOMe (1 eq, 135 mg) was added and the

mixture was heated to reflux. After 15 h, the ester hydrolyzed to the 2-(6-chloro-3-pyridyl)thiazole carboxylic acid. NaOMe (2 eq) was added and the reaction was heated at reflux for 18 h. The mixture was acidified to pH 5 with 5 concentrated HCl, extracted with EtOAc, washed with H₂O and brine; dried (MgSO₄) and concentrated *in vacuo* to give the desired carboxylic acid as a yellow solid. MS m/z: 237.1 (M+H).

10 **Preparation BE: 2-(2-Chloropyridin-4-yl)thiazole-4-carbonyl azide**

A mixture of 3-(3-chloro-4-pyridyl)-4-thiazole carboxylic acid (0.6 g, 2.5 mmol) and dry THF (20 mL) was cooled to 0°C with stirring. TEA (0.7 mL, 5.0 mmol) was 15 added and the reaction mixture was stirred for 20 min. Ethyl chloroformate (0.24 mL, 2.5 mmol) was added and the solution was stirred for 30 min. A solution of NaN₃ (174 mg, 2.7 mmol) in 3 mL of H₂O was added and the reaction mixture was warmed to RT. After 30 min, 10 mL of H₂O was 20 added and the mixture was extracted with EtOAc (3x), dried (MgSO₄) and concentrated *in vacuo* to give the title compound as a pink solid. MS m/z: 266.0 (M+H) +

25 **Preparation BF: Ethyl 2-(3-methoxyphenyl)-thiazole-4-carboxylate**

A suspension of 3-methoxyphenyl boronic acid (0.25 g, 1.65 mmol), ethyl 2-bromothiazole-4-carboxylate (0.33 g, 1.4 mmol), PdCl₂(dppf)₂ (0.11 g) and 2M Na₂CO₃ (aq) (2 mL) in DME (10 mL) was heated to reflux for 20 h. The mixture was 30 cooled to RT, filtered, concentrated by rotary evaporation and purified on silica gel (6:1 hexanes/EtOAc and 4:1 hexanes/EtOAc) to afford the title compound as a light-brown oil. EI-MS m/z 264 (M+H).

Preparation BG: 2-(3-Methoxyph nyl)thiazole-4-carboxylic acid

To a stirred solution of the ethyl 2-(3-methoxy-phenyl)thiazole-4-carboxylate (0.23 g, 0.87 mmol) in EtOH (10 mL) was added 1N NaOH (aq) (5 mL). The resulting mixture was heated to reflux until the starting material was consumed (2 h). The mixture was cooled to RT, acidified with 1N HCl (aq) and concentrated by rotary evaporation. The residue was extracted with CH₂Cl₂ (3x15mL). The extracts were combined, dried over MgSO₄, filtered and concentrated by rotary evaporation to afford the title compound as an off-white solid. EI-MS m/z 236 (M+H).
10

Preparation BH: Ethyl 2-(2-methoxyphenyl)-thiazole-4-carboxylate

A suspension of 2-methoxyphenyl boronic acid (0.25 g, 1.65 mmol), ethyl 2-bromothiazole-4-carboxylate (0.33 g, 1.4 mmol), PdCl₂(dppf)₂ (0.11 g, 0.14 mmol) and 2M Na₂CO₃ (aq) (2 mL) in DME (10 mL) was heated at reflux for 20 h, cooled to RT, filtered, concentrated by rotary evaporation and purified on silica gel (6:1 hexanes/EtOAc and 4:1 hexanes/EtOAc) to afford the title compound as a light-brown oil. EI-MS m/z 264 (M+H).
20

Preparation BI: 2-(2-Methoxyphenyl)thiazole-4-carboxylic acid

To a stirred solution of ethyl 2-(2-methoxy-phenyl)thiazole-4-carboxylate (0.27 g, 1.03 mmol) in EtOH (10 mL) was added 1N NaOH (aq) (5 mL). The resulting mixture was heated to reflux for 2 h. The mixture was cooled to RT, acidified with 1N HCl (aq) and concentrated by rotary evaporation. The residue was extracted with CH₂Cl₂ (3x15mL). The extracts were combined, dried over MgSO₄, filtered and

concentrated by rotary evaporation to afford the title compound as an off-white solid. EI-MS m/z 236 (M+H).

Preparation BJ: 2-[(4-Methoxyphenoxy)methyl]thiazole-4-

5 carboxylic acid

To a stirred solution of ethyl 2-(4-methoxyphenoxy)methyl]thiazole4-carboxylate (0.10 g, 0.34 mmol) in EtOH (5 mL) was added 1N NaOH (2.0 mL) and was heated to reflux until the starting material was consumed (2 h). The mixture was brought to RT, acidified with 1N HCl (pH 4.0) and concentrated by rotary evaporation. The residue obtained was partitioned between EtOAc (50 mL) and H₂O (30 mL). The organic phase was separated, dried over MgSO₄, filtered and concentrated by rotary evaporation to afford the title compound as a white solid. EI-MS m/z 266 (M+H).

Preparation BK: 2-Amino-thiazole-4-carboxylic acid ethyl ester hydrobromide

To a stirred suspension of thiourea (24.26 g, 0.319 mol) in 200 proof EtOH (350 mL) at RT, under N₂, ethyl bromopyruvate (62.16 g, 0.319 mol) was added dropwise. Upon completion the yellow solution was heated to 45°C for 15 h, then placed in a fridge overnight. The precipitate was filtered off and washed with cold EtOH (3 x 100 mL) to yield the title compound as a pale yellow amorphous solid. MS m/z: 173.1 (M+H), 195.1 (M+Na). Calc'd. for C₆H₉BrN₂O₂S - 253.12.

Preparation BL: 2-Bromothiazole-4-carboxylic acid

To a well stirred suspension of ethyl 2-aminothiazole-4-carboxylate hydrobromide (29.99 g, 0.17 mol) in 16% HBr(aq) (400 mL) at 0°C, a solution of NaNO₂ (12.49 g, 0.18 mol) in H₂O (22 mL) was added dropwise. The mixture was maintained at 0°C for an additional 35 min then CuBr (28.23 g, 0.20 mol) and an additional volume of 16% HBr(aq) (150

mL) were added. The ice bath was removed and the suspension heated to 70°C for 1 hr. The mixture was filtered hot. The filtrate was saturated with NaCl then extracted with EtOAc (2x400mL). The combined organic layers were dried over 5 MgSO₄, filtered and concentrated under reduced pressure. The crude brown oil/solid residue was used directly in the next step. A solution of the brown residue in EtOH (100 mL) and 1M NaOH (aq) (367 mL, 0.36 mol) was stirred and heated at reflux for 1 h. The reaction mixture was filtered then 10 extracted with EtOAc (100 mL). The aqueous layer was separated and concentrated under reduced pressure to remove the remaining EtOH. The aqueous solution was acidified to pH 1 with 2N HCl(aq). The solid was filtered off and air dried to yield the title compound as a beige amorphous 15 solid. MS m/z: 208 (M+H) 210 (M+3).

Preparation BM: Ethyl 2-(2,6-dichloro-4-pyridyl)thiazole-4-carboxylate

2,6-Dichloropyridine-4-thiocarboxamide (1.0 g, 4.83 20 mmol) was dissolved in dry 1,4-dioxane followed by adding ethyl bromopyruvate (0.9 mL, 7.24 mmol) and pyridine (0.4 mL, 4.83 mmol). The resulting mixture was heated to reflux under N₂ for 5 h. After cooling to RT, solvent was removed. The residue was extracted with CHCl₃. The organic layer was 25 washed with H₂O and brine, dried over MgSO₄, and concentrated to give a brownish solid. This crude was purified by chromatography on silica gel. Elution with hexane:acetone (90:10) gave a title compound as yellow solid. MS m/z: 303 (M+H). Calc'd. for C₁₁H₈Cl₂N₂O₂S - 30 303.16.

Preparation BN: 2-(2,6-Dichloro-4-pyridyl)thiazole-4-carboxylic acid

2-(2,6-Dichloropyridin-4-yl)-ethylthiazolo-4-carboxylate (500 mg, 1.65 mmol) was dissolved in MeOH (10 mL) followed by adding 1N NaOH (2.5 mL, 2.47 mmol). The resulting mixture was stirred at RT for 4 h. The pH was 5 adjusted to 5 using 1N HCl. The solvent was removed *in vacuo* and the residue was partitioned between EtOAc and H₂O. The aqueous layer was extracted more with EtOAc. The combined organic layers was dried over MgSO₄ and concentrated to give a white solid. MS *m/z*: 275.1 (M+H).
10 Calc'd. for C₉H₄Cl₂N₂O₂S - 275.11.

Preparation BO: Ethyl 6-[2-(2,2,2-trifluoroethoxy)-3-pyridyl]thiazole-4-carboxylate

6-(2,2,2-Trifluoroethoxy)pyridine-3-thiocarboxamide (800 mg, 3.4 mmol), ethyl bromopyruvate (0.9 mL, 6.8 mmol), and pyridine (0.3 mL, 3.4 mmol) were heated at reflux in dry 1,4-dioxane (20 mL) to yield title compound as pale yellow solid. MS *m/z*: 333.1 (M+H). Calc'd. for C₁₃H₁₁F₃N₂O₃S - 332.3.

20
Preparation BP: 6-[2-(2,2,2-trifluoroethoxy)-3-pyridyl]thiazole-4-carboxylic acid

Ethyl 6-[2-(2,2,2-trifluoroethoxy)-3-pyridyl]thiazole-4-carboxylate (750 mg, 2.25 mmol) and 1N NaOH (3.4 mL, 3.4 mmol) were dissolved in MeOH (10 mL) to afford the title compound as a white solid. MS *m/z*: 305.1 (M+H). Calc'd. for C₁₁H₇F₃N₂O₃S - 304.25.

Preparation BQ: 2-(Phenoxy)thiazole-4-carboxylic acid

30 A mixture of ethyl 2-phenoxythiazole-4-carboxylate (0.17 g, 0.68 mmol) and LiOH monohydrate (0.14 g, 3.40 mmol) in 2 mL of MeOH, 2 mL of H₂O, and 2 mL of THF was stirred at RT overnight, the solvents were removed *in vacuo* and the residue was diluted with water. The aqueous mixture was

acidified with 1N HCl (aq) to pH=1-2, then extracted with EtOAc, the combined organic portions were washed with brine, dried over MgSO₄, filtered, removal of the solvents in vacuo yielded the title compound as a white solid. EI-MS = 222.4
5 (M+H) +. Calc'd for C₁₀H₇NO₃S: 221.01.

Preparation BR: 3-(3-Nitrophenyl)pyridine

To a 1-iodo-3-nitrobenzene (1.0 g, 4.01 mmol) in dry DME (20 mL) was added pyridine-3-boronic acid (641 mg, 5.22
10 mmol), PdCl₂dppf (327 mg, 0.40 mmol), and 2M Na₂CO₃ (3.0 mL). The resulting mixture was heated to reflux under N₂ for 15 h. Solvent was separated from inorganic solid by filtration. The solvent was removed and the residue was extracted with CHCl₃. The organic layer was washed with
15 water, brine, and dried over MgSO₄. The solvent was removed to give dark brown solid which was purified by chromatography on silica gel. Elution with Hexane:acetone mixture (80:20) gave the final compound as a tan solid. MS m/z: 201.3 (M+H). Calc'd. for C₁₁H₈N₂O₂ - 200.23.

20

Preparation BS: 3-(3-Aminophenyl)pyridine

To a pre-hydrogenated solution of Pd(OH)₂ (298 mg, 2.12 mmol) in EtOH (10 mL) was added 3-(3-pyrid-1-yl)-1-nitrobenzene (440 mg, 2.12 mmol) in EtOH (10 mL). The resulting mixture was stirred at RT under H₂ for 2 h. Solvent was separated from Pd(OH)₂ by filtration through Celite®. Solvent was then removed to give final compound as pale yellow solid. MS m/z: 171.3 (M+H). Calc'd. for C₁₁H₁₀N₂ - 170.22.

30

Preparation BT: 2,2-Dimethyl-N-[6-(2,2,6,6-tetramethyl-piperidin-1-ylmethyl)-pyridin-2-yl]-propionamide:

2,2,6,6-Tetramethylpiperidine (0.17 mL, 1.0 mmol) was added to a solution of N-pivaloyl-2-amino-6-

bromomethylpyridine (180 mg, 0.66 mmol; M. Papadopoulou, et al., *J. Het. Chem.*, 1995, 32, 675-681) in DMF (10 mL) at 25°C and the resulting mixture was stirred for 12 h. The reaction mixture was partitioned between H₂O (15 mL) and 5 EtOAc (20 mL) and the organics collected. The organics were washed with H₂O (20 mL) followed by brine (20 mL) and dried over MgSO₄. Concentration *in vacuo* gave a colorless oil. MS *m/z*: 330.1 (M-H). Calc'd for C₂₀H₃₃N₃O - 331.50.

10 **Preparation BU: 6-(2,2,6,6-Tetramethyl-piperidin-1-ylmethyl)-pyridin-2-ylamine:**
KOH (1.68 g, 33.5 mmol) in MeOH (100 mL) was added to 2,2-dimethyl-N-[6-(2,2,6,6-tetramethyl-piperidin-1-ylmethyl)-pyridin-2-yl]-propionamide (150 mg, 0.45 mmol) and 15 the resulting mixture was heated at reflux for 12 h. After cooling to 25°C, the mixture was neutralized to pH 7-8 with concentrated HCl and extracted with CHCl₃ (3 x 75 mL). The organics were combined and dried over MgSO₄. Concentration *in vacuo* gave a pale yellow solid. MS *m/z*: 247.7 (M⁺).
20 Calc'd for C₁₅H₂₅N₃ - 247.38.

Preparation BV: (2-Chloro-pyridin-4-yl)-piperidin-1-yl-methanone
To 2-chloroisonicotinic acid (1.0 g, 6.35 mmol) in dry 25 CH₂Cl₂ (50 mL) was added piperidine (1.3 mL, 12.69 mmol), DIEA (2.2 mL, 12.69 mmol), HATU (1.2 g, 3.17 mmol), and EDCI (1.3 g, 6.98 mmol). The mixture was stirred under N₂ at RT for 15 h. Solvent was removed and the crude compound was purified by chromatography on silica gel. Elution with 30 hexane:acetone mixture (80:20) gave a white solid. MS *m/z*: 225.1 (M+H). Calc'd. for C₁₁H₁₃ClN₂O - 224.07.

Preparation BW: (2-Amino-pyridin-4-yl)-piperidin-1-yl-methanone

NH₄OH (25 mL) and Cu powder (100 mg) were added to a solution of (2-amino-pyridin-4-yl)-piperidin-1-yl-methanone (1.0 g, 4.45 mmol) in IpOH (15 mL) and the mixture was heated at 100 °C for 48 h in a sealed tube. After cooling to RT, the mixture was partitioned between H₂O and CHCl₃. The aqueous layer was extracted with more CHCl₃ (3 x 20 mL). The combined organic layers was washed with brine, and dried over MgSO₄. Concentration in vacuo gave a light brown solid. MS m/z: 206.3 (M+H). Calc'd. for C₁₁H₁₅N₃O - 10 205.12.

Preparation BX: 4-Piperidin-1-ylmethyl-pyridin-2-ylamine

To a stirred solution of (2-amino-pyridin-4-yl)-piperidin-1-yl-methanone (100 mg, 0.487 mmol) in dry THF (10 mL) at 0°C was added LAH (1.5 mL, 1.46 mmol) dropwise. The mixture was heated to reflux for 20 h. The resulting mixture was cooled to 0°C and quenched with H₂O (1.5 mL) dropwise followed by 10% NaOH (1.5 mL). Solvent was removed and the residue was partitioned between H₂O and CHCl₃. The organic layer was washed with H₂O, brine, dried over MgSO₄. Concentration in vacuo gave a light brown liquid. MS m/z: 192.2 (M+H). Calc'd. for C₁₁H₁₇N₃ - 191.14.

Preparation BY: 4-Diethylaminomethyl-pyridin-2-ylamine

25 Prepared in a manner similar to that described for 4-piperidin-1-ylmethyl-pyridin-2-ylamine. MS m/z: 180.2 (M+H). Calc'd. for C₁₀H₁₇N₃ - 179.14.

Preparation BZ: [6-(2,6-Dimethyl-piperidin-1-ylmethyl)-30 pyridin-2-yl]-carbamic acid tert-butyl ester

2,6-Dimethylpiperidine (0.24 mL, 1.74 mmol) was added to a solution of (6-bromomethyl-pyridin-2-yl)-carbamic acid tert-butyl ester (250 mg, 0.87 mmol) in DMF (10 mL) followed by heating at 50°C and the resulting mixture was stirred for

18 h. The resulting mixture was partitioned between water (10 mL) and CHCl_3 (20 mL). The organic layer was washed with H_2O , brine, and dried over MgSO_4 . Concentration *in vacuo* gave a pale yellow solid. MS m/z: 320.3 (M+H).
5 Calc'd. for $\text{C}_{18}\text{H}_{29}\text{N}_3\text{O}_2$ - 319.23.

Preparation CA: 6-(2,6-Dimethyl-piperidin-1-ylmethyl)-pyridin-2-ylamine

HCl (1.25 mL, 1.25 mmol) in MeOH (15 mL) was added to
10 [6-(2,6-dimethyl-piperidin-1-ylmethyl)-pyridin-2-yl]-carbamic acid tert-butyl ester (200 mg, 0.63 mmol) followed by heating at 40°C for 18 h. The resulting mixture was cooled to RT and basified to pH 9 with 2 N NaOH. The mixture was extracted with CHCl_3 (3 x 20 mL). The combined
15 organic layers was dried over MgSO_4 and concentrated *in vacuo* to give a yellow oil. MS m/z: 220.2 (M+H). Calc'd. for $\text{C}_{13}\text{H}_{21}\text{N}_3$ - 219.17.

Preparation CB: 1-(6-Bromo-pyridin-2-yl)-ethanol

20 6-Bromo-2-pyridine carboxaldehyde (1.0 g, 5.37 mmol) in dry THF (20 mL) was cooled to -78°C followed by adding MeMgI (2.0 mL, 5.91 mmol) dropwise via the addition funnel. The cooling bath was removed. The resulting mixture was stirred for 1 h then quenched with sat. NH_4Cl . Solvent was
25 removed. The residue was partitioned between water and CHCl_3 . The organic layer was washed with H_2O , brine, dried over MgSO_4 . Solvent was removed and crude compound was purified by chromatography on silica gel. Elution with hexane:acetone mixture (70:30) gave a white solid. MS m/z:
30 201.9 (M+H). Calc'd. for $\text{C}_7\text{H}_8\text{BrNO}$ - 200.98.

Preparation CC: 1-(6-Bromo-pyridin-2-yl)-ethanone

Oxalyl chloride (2.1 mL, 3.81 mmol) in dry CH_2Cl_2 was cooled to -70°C followed by adding DMSO (0.6 mL, 8.39 mmol)

dropwise. After stirred for 5 min under -60°C, 1-(6-bromo-pyridin-2-yl)-ethanol (770 mg, 3.81 mmol) in dry CH₂Cl₂ (10 mL) was added dropwise. After stirred for 30 min, TEA (2.7 mL, 19.83 mmol) was added and the resulting mixture was 5 warmed to RT and stirred for 1 h. The reaction mixture was quenched with H₂O. The organic layer was washed with H₂O, brine, and dried over MgSO₄. Solvent was removed and the crude compound was purified by chromatography on silica gel. Elution with hexane:acetone mixture (90:10) gave a white 10 solid. MS m/z: 200.3 (M+H). Calc'd. for C₇H₈BrNO - 198.96.

Preparation CD: 2-Bromo-6-(1-piperidin-1-yl-ethyl)-pyridine

To a stirred solution of 1-(6-bromo-pyridin-2-yl)-ethanone (600 mg, 3.01 mmol) in dry CH₂Cl₂ (20 mL) was added 15 piperidine (0.5 mL) followed by NaBH(OAc)₃ (1.3 g, 12.06 mmol) and HOAc (0.7 mL, 6.03 mmol). The mixture was heated at 40°C for 72 h. The reaction was quenched with 2M Na₂CO₃ and stirred 1 h. The organic layer was collected, dried over MgSO₄ and concentrated in vacuo. This crude compound 20 was purified by chromatography on silica gel. Elution with hexane:acetone mixture (90:10) gave a light yellow solid. MS m/z: 269.2 (M+H). Calc'd. for C₁₂H₁₇BrN₂ - 268.06.

Preparation CE: 2-Hydroxymethyl-piperidine-1-carboxylic acid tert-butyl ester

Piperidine-1,2-dicarboxylic acid 1-tert-butyl ester (50 g, 218.1 mmol) in dry THF (300 mL) was cooled to -78°C followed by adding BH₃-THF solution (261.7 mL, 260.0 mmol) 30 dropwise over 1 h. The resulting mixture was warmed to RT and stirred for 48 h. The reaction was quenched with HOAc/H₂O (1:1 ratio, 100 mL). The resulting mixture was partitioned between EtOAc and sat. NaHCO₃. The organic layer was washed with more sat. NaHCO₃, H₂O, brine, and

dried over $MgSO_4$. Concentration in vacuo gave a white solid. MS m/z: 216.2 (M+H). Calc'd. for $C_{11}H_{21}NO_3$ - 215.15.

Preparation CF: 2-Formyl-piperidine-1-carboxylic acid tert-butyl ester

5

In a manner similar to that described in Preparation CC, 2-hydroxymethyl-piperidine-1-carboxylic acid tert-butyl ester (500 mg, 2.32 mmol) was added to a mixture of oxalyl chloride (1.3 mL, 2.55 mmol) and DMSO (0.36 mL, 5.11 mmol) 10 followed by adding TEA (1.7 mL, 12.07 mmol) to give a white solid. MS m/z: 214.2 (M+H). Calc'd. for $C_{11}H_{19}NO_3$ - 213.14.

Preparation CG: 2-[(6-Amino-pyridin-2-ylamino)-methyl]-piperidine-1-carboxylic acid tert-butyl ester

15 In a manner similar to that described in Preparation CD, 2-formyl-piperidine-1-carboxylic acid tert-butyl ester (360 mg, 1.69 mmol) was treated with 2,6-diaminopyridine (184 mg, 1.69 mmol) and stirred at RT to give a light brown oil. MS m/z: 307.3 (M+H). Calc'd. for $C_{16}H_{26}N4O_2$ - 306.21.

20

Preparation CH: 5-Cyano-indole-1-carboxylic acid tert-butyl ester

25 To a solution of 5-cyanoindole (9.76 g, 68.7 mmol), 100 mL of anhydrous CH_3CN , and DMAP (423 mg, 3.5 mmol) was added di-tert-butyl dicarbonate (15.78 g, 72.3 mmol). The resulting solution was stirred for 18 h then concentrated in vacuo. The resulting solid was redissolved in $EtOAc$ (350 mL) and washed with 1N HCl (aq) (2 X 25 mL). The acidic aqueous solution was extracted with $EtOAc$ (2X). The 30 combined $EtOAc$ layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give a light yellow solid. MS m/z: 243 (M+1). Calc'd for $C_{14}H_{14}N_2O_2$ - 242.47.

Preparation CI: 5-Thiocarbamoyl-indole-1-carboxylic acid
tert-butyl ester

H₂S (g) was bubbled through a solution of 5-cyano-indole-1-carboxylic acid *tert*-butyl ester (15.71 g, 64.8 mmol), 120 mL of pyridine, and TEA (27.5 mL, 197.3 mmol). The reaction was followed by LC-MS and concentrated in vacuo upon completion to give a black solid. MS *m/z*: 277 (M+1). Calc'd for C₁₄H₁₆N₂O₂S - 276.36.

10 Preparation CJ: 5-(4-Ethoxycarbonyl-thiazol-2-yl)-indole-1-
carboxylic acid *tert*-butyl ester

To a solution of 5-thiocarbamoyl-indole-1-carboxylic acid *tert*-butyl ester (13.16 g, 47.6 mmol) and 250 mL of EtOH was added ethyl bromopyruvate (6.05 mL, 48.2 mmol). The resulting solution was stirred at 60°C for 1.5 h, then concentrated in vacuo. The resulting solid was purified by flash chromatography on silica gel using 5% EtOAc/hexane → 80% EtOAc/hexane → CH₂Cl₂ as the eluant to give a white solid. MS *m/z*: 373 (M+1). Calc'd for C₁₉H₂₀N₂O₄S - 372.44.

20 Preparation CK: 5-(4-Carboxy-thiazol-2-yl)-indole-1-
carboxylic acid *tert*-butyl ester

To a solution of 5-(4-ethoxycarbonyl-thiazol-2-yl)-indole-1-carboxylic acid *tert*-butyl ester (3.34 g, 9.0 mmol) and 125 mL of THF was added 1N NaOH (aq) (30.0 mL, 30.0 mmol). The solution was stirred for 24 h then concentrated in vacuo. The crude solid was redissolved in H₂O and acidified with 5% KHSO₄. The solid was filtered and dried in vacuo at 60°C to give a pinkish-white solid. MS *m/z*: 345 (M+1). Calc'd for C₁₇H₁₆N₂O₄S - 344.39.

Preparation CL: 2-Bromo-thiazole-4-carboxylic acid ethyl
ster

To a stirred mixture of 2-amino-thiazole-4-carboxylic acid ethyl ester hydrobromide (10 g, 58 mmol), CuSO₄ (26.9 g, 168 mmol) and NaBr (22.7 g, 221 mmol) in 9M H₂SO₄ (aq) (120 mL) at -5°C - 0°C, a pre-cooled solution of NaNO₂ (4.4 g, 64 mmol) in H₂O (40 mL) was added at such a rate to maintain the temperature at or below 0°C. After complete addition the mixture was maintained at 0°C for another 30 min then warmed to RT over 2.5 h. The reaction mixture was diluted with H₂O (120 mL) and extracted with Et₂O (3 x 100 mL). The aqueous layer was separated, basified to pH 12 with 5N NaOH (aq), then extracted with Et₂O (2 x 100 mL). The organic layers were combined, dried over Na₂SO₄, filtered and the solvent evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (1:9, EtOAc:hexane) to yield the title compound as a white amorphous solid. MS *m/z*: 235.8, 237.8 (M+H). Calc'd. for C₆H₆BrNO₂S - 234.93.

Preparation CM: 2-Chloro-thiazole-4-carboxylic acid ethyl ester

2-Amino-thiazole-4-carboxylic acid ethyl ester hydrobromide (34.46 g, 0.137 mol) was basified with a saturated solution of NaHCO₃ (aq) (300 mL) and extracted with EtOAc (8 x 300mL). The combined organic layers were dried over Na₂SO₄, filtered and the solvent evaporated *in vacuo* to liberate the free base. To a well stirred suspension of the free base in 9M H₂SO₄ (aq) (500 mL) at 0°C to -5°C, CuSO₄ (63.34 g, 0.397 mol) and NaCl (30.39 g, 0.520 mol) were added, followed by the dropwise addition of a solution of NaNO₂ (10.39 g, 0.151 mol) in H₂O (150 mL), over 45 min. The mixture was maintained at 0°C for 1 h then warmed to RT. After 1 h at RT the reaction mixture was diluted with H₂O (2 L) and extracted with Et₂O (3 x 300mL). The combined organic layers were dried over Na₂SO₄, filtered

and the solvent was evaporated *in vacuo* to yield the title compound as a pale yellow amorphous solid (sufficiently pure to be used directly in the next step). MS *m/z*: 192.0 (M+H). Calc'd. for C₆H₆ClNO₂S - 191.64.

5

Preparation CN: 2-Chloro-thiazole-4-carboxylic acid

To a stirred solution of 2-chlorothiazole-4-carboxylic acid ethyl ester (20.49 g, 0.107 mol) in THF (180 mL) at RT, a 1M solution of LiOH (aq) (160 mL, 0.160 mol) was added.

10 The resulting solution was heated to 65°C for 1 h. The solvent was evaporated *in vacuo*. The residue was treated with brine (100 mL) and acidified to pH 1 with 1M HCl (aq). The precipitate was filtered off, washed with H₂O (2 x 50 mL) and Et₂O (2 x 50 mL) and dried in a vacuum oven at 60°C
15 for 62 h to yield the title compound as a pale yellow solid. MS *m/z*: 164.1 (M+H). Calc'd. for C₄H₂ClNO₂S - 163.58.

Preparation CO: 2-Chloro-thiazole-4-carbonyl azide

To a stirred solution of 2-chlorothiazole-4-carboxylic acid (15.30 g, 94 mmol) in anhydrous THF (200 mL) at 0°C, under nitrogen, TEA (26.1 mL, 187 mmol) was added. After 30 min ethyl chloroformate (9.39 mL, 98 mmol) was added dropwise over 10 min. After 25 min a solution of NaN₃ (6.38 g, 98 mmol) in H₂O (110 mL) was added. The mixture was
25 warmed to RT over 1 h then diluted with H₂O (500 mL). The precipitate was filtered off and air dried to yield the title compound as a white amorphous solid. MS *m/z*: 189.3 (M+H). Calc'd. for C₄HClN₄OS - 188.60.

30 **Preparation CP: 2-Bromo-thiazole-4-carbonyl azide**

To a stirred solution of 2-bromo-thiazole-4-carboxylic acid (5.33 g, 25.7 mmol) in anhydrous THF (40 mL) at 0°C, under N₂, TEA (7.18 mL, 51.5 mmol) was added. After 30 min ethyl chloroformate (2.59 mL, 27.0 mmol) was added dropwise

over 10 min. After 25 min a solution of NaN₃ (1.76 g, 27.0 mmol) in H₂O (12 mL) was added. The mixture was warmed to RT over 1 h then diluted with H₂O (100 mL). The precipitate was filtered off and air dried to yield the title compound 5 as a white amorphous solid. MS m/z: 233.2, 235.2 (M+H). Calc'd. for C₄HBrN₄OS - 233.05.

Preparation CQ: 3-(Benzylloxycarbonylamino-methyl)-piperidine-1-carboxylic acid tert-butyl ester

10 To a stirred solution of 3-(aminomethyl)-1-N-Boc-piperidine (1.64 g, 7.65 mmol) and TEA (1.6 mL, 11 mmol) in THF (5 mL) at 0°C, benzyl chloroformate (1.15 mL, 8.04 mmol) was added dropwise. The reaction was maintained at 0°C for 1 h, then warmed to RT overnight. The solvent was 15 evaporated *in vacuo*. The residue was taken up in a saturated solution of NH₄Cl (aq) (15 mL) and extracted with EtOAc (10 mL). The organic layer was separated, dried over MgSO₄, filtered and the solvent was evaporated *in vacuo*. The residue was purified by flash chromatography on silica 20 gel (1:4, EtOAc:hexane) to yield the title compound as a colorless oil. MS m/z: 349.3 (M+H). Calc'd. for C₁₉H₂₈N₂O₄ - 348.44.

Preparation CR: Piperidin-3-ylmethyl-carbamic acid benzyl ester

25 To a stirred solution of 3-(benzyloxycarbonylamino-methyl)-piperidine-1-carboxylic acid tert-butyl ester (983 mg, 2.82 mmol) in anhydrous CH₂Cl₂ (10 mL) at RT, under N₂, TFA (3 mL) was added. After 2.5 h the solvent was 30 evaporated *in vacuo* and the residue was dissolved in EtOAc (20 mL). The organic layer was washed with a saturated solution of NaHCO₃ (aq) (30 mL), separated, dried over Na₂SO₄, filtered and the solvent evaporated *in vacuo* to

yield the title compound as a pale yellow oil. MS *m/z*: 249.0 (M+H). Calc'd. for C₁₉H₂₈N₂O₄ - 248.32.

Preparation CS: 2-[3-(Benzylloxycarbonylamino-methyl)-

piperidin-1-yl]-thiazole-4-carboxylic acid ethyl ester

To a stirred solution of piperidin-3-ylmethyl-carbamic acid benzyl ester (43 mg, 0.17 mmol) in CH₃CN (5 mL), at RT under N₂, K₂CO₃ (26 mg, 0.19 mmol) and 2-bromo-thiazole-4-carboxylic acid ethyl ester (41 mg, 0.17 mmol) were added. The resulting mixture was heated at reflux for 29 h. The solvent was evaporated *in vacuo*. The residue was treated with a saturated solution of NH₄Cl (aq) (10 mL) and extracted with EtOAc (10 mL). The organic layer was separated, dried over Na₂SO₄, filtered and the solvent evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (1:2, EtOAc:hexane) to yield the title compound as a colorless oil. MS *m/z*: 404.2 (M+H). Calc'd. for C₂₀H₂₅N₃O₄S - 403.50.

20 Preparation CT: 2-[3-(Benzylloxycarbonylamino-methyl)-

piperidin-1-yl]-thiazole-4-carboxylic acid

To a stirred solution of 2-[3-(benzylloxycarbonylamino-methyl)-piperidin-1-yl]-thiazole-4-carboxylic acid ethyl ester (439 mg, 1.15 mmol) in THF (5 mL) at RT, a 1M solution of LiOH (aq) (1.72 mL, 1.72 mmol) was added. After 16 h the solvent was evaporated *in vacuo*. The residue was treated with brine (25 mL) and acidified to pH 1 with 2N HCl (aq) then extracted with EtOAc (30 mL). The organic layer was separated, dried over Na₂SO₄, filtered and the solvent evaporated *in vacuo* to yield the title compound as a colorless oil. MS *m/z*: 355.9 (M+H). Calc'd. for C₁₆H₂₅N₃O₄S - 355.45.

Preparation CU: Cyclopropanecarbothioamide

To a solution of cyclopropanecarboxamide (0.525 g, 6.169 mmol) and Na_2CO_3 (0.654 g, 6.169 mmol) in THF (100 mL) was added solid P_2S_5 (2.742 g, 6.169 mmol). The reaction was brought to reflux and kept at this temperature for 2 h. The 5 reaction mixture was cooled to RT, filtered through Celite[®] and concentrated *in vacuo* to yield crude cyclopropane-carbothioamide (used for the next step without purification). MS *m/z*: 102.1 (M+H) Calc'd. for $\text{C}_4\text{H}_8\text{NS}$ - 102.0.

10

Preparation CV: Ethyl 2-cyclopropyl-thiazole-4-carboxylate

To a solution of cyclopropanecarbothioic acid amide (1.18 g, 0.012 mol) in EtOH (60 mL) was added ethylbromopyruvate (1.71 mL, 0.012 mol) at RT and the 15 mixture was brought to reflux and kept at this temperature for 3 h. The reaction mixture was cooled to RT and evaporated to dryness. Crude compound was dissolved in cold CH_3CN (5 mL) and filtered. The filtrate was concentrated *in vacuo* and the resulting residue was purified by column 20 chromatography eluting with hexanes:EtOAc (4:1) to give ethyl 2-cyclopropyl-thiazole-4-carboxylate. MS *m/z*: 197.9 (M+H) Calc'd. for $\text{C}_9\text{H}_{12}\text{NO}_2\text{S}$ - 198.0.

Preparation CW: 2-Cyclopropyl-thiazole-4-carboxylic acid

25 To a mixture of ethyl 2-cyclopropyl-thiazole-4-carboxylate (0.443 g, 2.249 mmol) and LiOH monohydrate (0.472 g, 11.243 mmol) was added a mixture of THF/MeOH/ H_2O (3:1:1, 50 mL). The reaction was stirred at RT for 24 h. The solution was acidified by addition of conc. HCl (0.1 mL) and 30 the volatiles were removed. Remaining aqueous solution was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to dryness. MS *m/z*: 169.9 (M+H) Calc'd. for $\text{C}_7\text{H}_7\text{NO}_2\text{S}$ - 170.0.

Pr paration CX: 2-Cyclopropyl-thiazol -4-carbonyl azide

To a solution of 2-cyclopropyl-thiazole-4-carboxylic acid (0.360 g, 2.130 mmol) and TEA (0.59 mL, 4.260 mmol) in THF (10 mL) at 0° C, was added ethylchloroformate (0.22 mL, 2.343 mmol) and the mixture was stirred for 30 min. A solution of NaN₃ (0.152 g, 2.343 mmol) in H₂O (10 mL) was added to this mixture and warmed to RT. After 1 h, the reaction mixture was diluted with H₂O (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over Na₂SO₄ and evaporated to dryness. MS m/z: 195.0 (M+H) Calc'd. for C₇H₇N₄OS - 195.0.

Preparation CY: 2-tert-Butyl-thiazole-4-carbonylazide

Synthesized from 2,2-dimethylpropionamide following preparations CU-CX. MS m/z: 211.3 (M+H) Calc'd. for C₈H₁₁N₄OS - 211.0.

Preparation CZ: 3-Sulfamoylthiobenzamide

3-Cyanobenzenesulfonamide (12.6 g, 0.067 mol) was added to a solution of TEA (0.8 mL), dry pyridine (0.5 mL) and benzene (30 mL) at RT and cooled to 0°C. H₂S was bubbled through the solution for 20 min. The reaction was stirred at RT for 20 h. The resulting solid was dissolved in MeOH (30 mL) and transferred for the next step. LC-MS m/z: 217 (M+H).

Preparation DA: 2-(3-Sulfamoyl-phenyl)-thiazole-4-carbonylazide

Synthesized from 3-sulfamoylthiobenzamide following preparations CV-CX. MS m/z: 310.2 (M+H). Calc'd. for C₁₀H₈N₅O₃S₂ - 310.0.

Preparation DB: Ethyl 2-cyclopropylethynyl-thiazole-4-carboxylate

To a solution of bromothiazole (319.5 mg, 1.353 mmol), Pd(PhCN)₂Cl₂ (155.7 mg, 0.406 mmol), CuI₂ (51.5 mg, 0.271 mmol) and tri-*t*-butylphosphine (0.2 M in toluene, 4.4 mL, 0.880 mmol) in dioxane (10 mL) was added DEA (0.21 mL, 2.030 mmol) and ethynylcyclopropane (107.2 mg, 1.624 mmol). The reaction mixture was stirred at RT for 12 h. Volatiles were removed in vacuo and was passed through a pad SiO₂ (elution with EtOAc). Chromatography (Hexanes: EtOAc, 9:1) gave pure ethyl 2-cyclopropylethynyl-thiazole-4-carboxylate. MS *m/z*: 10 222.2 (M+H) Calc'd. for C₁₁H₁₂NO₂S - 222.0.

Preparation DC: 2-Cyclopropylethynyl-thiazole-4-carbonyl azide

Prepared from ethyl 2-cyclopropylethynyl-thiazole-4-carboxylate following preparations CW-CX. MS *m/z*: 15 219.3 (M+H) Calc'd. for C₉H₇N₄OS - 219.0.

Preparation DD: (6-Bromo-pyridin-2-ylmethyl)-isopropyl-amine

To a stirred solution of 6-bromo-pyridine-2-carbaldehyde (1.06 g, 5.73 mmol) in dry CH₂Cl₂ (30 mL) was added isopropylamine (0.51 mL, 6.02 mmol). The mixture was stirred at RT and under N₂ for 30 min followed by the addition of NaBH(OAc)₃ (2.42 g, 11.46 mmol) and HOAc (1.3 mL, 22.92 mmol). The resulting cloudy light-yellow solution was stirred at RT and under N₂ for 15 h. A 10% solution of Na₂CO₃ (50 mL) was added to the mixture and stirred for 30 min. The organic phase was separated, washed with H₂O, brine, dried over MgSO₄ and concentrated to afford a light 25 yellow-oil without further purification. MS *m/z*: 229.1 (M+H). Calc'd for C₉H₁₃BrN₂: 228.03.

Preparation DE: (6-Bromo-pyridin-2-ylmethyl)-isopropyl-carbamic acid *tert*-butyl ester

To a stirred solution of (6-bromo-pyridin-2-ylmethyl)-isopropyl-amine in CH_2Cl_2 (100 mL) was added $(\text{Boc})_2\text{O}$ (10.2 g, 46.7 mmol). The resulting mixture was stirred at RT for 3 days. The mixture was concentrated and purified by 5 chromatography on silica gel using 6:1 Hex/EtOAc as eluent to afford a very pale yellow-oil which solidified once cooled to RT. MS m/z: 329.3 ($\text{M}+\text{H}$). Calc'd for $\text{C}_{14}\text{H}_{21}\text{BrN}_2\text{O}_2$: 328.08.

10 **Preparation DF: 4-pyrrolidin-1-ylmethylphenol**

To a stirred solution of 4-hydroxylbenzaldehyde (10 g, 81.9 mmol) in anhydrous CH_2Cl_2 (500 mL) at RT, under N_2 , pyrrolidine (10.2 mL, 122.9 mmol) was added, followed by 15 $\text{NaBH}(\text{OAc})_3$ (34.6 g, 163.9 mmol) and AcOH (19.7 g, 327.8 mmol). After the mixture was stirred at RT for 24 h, a saturated solution of NaHCO_3 (aq) (150 mL) was added. The mixture was vigorously stirred for an additional 1 h and then extracted with CH_2Cl_2 (3X200 mL). The combined organic layer was washed with brine (300 mL), dried over MgSO_4 , 20 filtered and concentrated under reduced pressure to yield the title compound as amber oil. This was used crude in the next step. MS m/z: 178 ($\text{M}+1$). Calc'd for $\text{C}_{11}\text{H}_{15}\text{NO}$ - 177.2.

25 **Preparation DG: 2-Bromo-6-(4-pyrrolidin-1-ylmethylphenoxy)pyridine**

To a stirred suspension of NaH (2.6 g, 108.5 mmol) in 30 DMF (300 mL) at 0°C , under N_2 , a solution of 4-pyrrolidin-1-ylmethylphenol (16 g, 90.4 mmol) was added slowly. After stirring at 0°C for 30 min, 2,6-dibromopyridine (23.6 g, 99.4 mmol) was added and the resulting mixture was heated at 95°C for 20 h. After cooling to RT, 200 mL of H_2O was added and the mixture was extracted with EtOAc (3X300 mL). The combined organic layer was washed with brine (3X400 mL), dried over MgSO_4 , filtered and concentrated under reduced

pressure to yield the title compound as an amber solid. This was used crude in the next step. MS m/z: 333 (M+1). Calc'd for $C_{16}H_{17}BrN_2O$ - 333.2

5 **Preparation DH: 2-Amino-6-(4-pyrrolidin-1-ylmethylphenoxy)pyridine**

A mixture of 2-bromo-6-(4-pyrrolidin-1-ylmethylphenoxy)pyridine (20 g) and Cu powder (1 g) in concentrated NH_4OH (250 mL, aq) and $IpOH$ (60 mL) was heated 10 at 100°C in a sealed flask for 48 h. After cooling to RT, brine (300 mL) was added and the mixture was extracted with EtOAc (3X200 mL). The combined organic layer was washed with brine (300 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residues were filtered through 15 silica gel pad eluting with $MeOH/CH_2Cl_2$ (5%). The filtrate was concentrated to dryness, then 50 mL of $MeOH$ was added. After stirring for a while the solid was filtered to give the title compound. MS m/z: 270 (M+1). Calc'd for $C_{16}H_{19}N_3O$ - 269.3

20

Preparation DI: 5-tert-Butyl-oxazole-2-carboxylic acid ethyl ester

The mixture of N-(3,3-dimethyl-2-oxo-butyl)-oxalamic acid ethyl ester (0.79 g, 3.67 mmol) and phosphorus oxychloride (2.0 mL, 22.0 mmol) was stirred at 105°C under N_2 for 2 h, cooled to RT, quenched slowly with ice-water, extracted with EtOAc. The combined organic portions were washed with brine, dried with Na_2SO_4 , removal of the solvents gave a dark brownish oil which was purified by 30 flash column chromatography to yield the title compound. MS m/z: 197.9 (M+H). Calc'd for $C_{10}H_{15}NO_3$ - 197.23

Preparation DJ: 5-tert-Butyl-oxazole-2-carboxylic acid amide

The mixture of 5-tert-butyl-oxazole-2-carboxylic acid 35 ethyl ester (0.52 g, 2.64 mmol) and NH_3 (2.0M solution in

MeOH, 6.6 mL, 13.2 mmol) was stirred at RT under N₂ for 20 h. The solvents were removed under reduced pressure and the residue was dissolved in EtOAc washed with brine, dried with Na₂SO₄ and filtered. Removal of the solvents afforded the 5 title compound as a white solid. MS m/z: 169.2 (M+H). Calc'd for C₈H₁₂N₂O₂ - 168.19

Preparation DK: 5-tert-Butyl-oxazole-2-carbothioic acid amide

10 In a manner similar to that described in preparation BB, the title compound was isolated as a yellow solid. MS m/z: 185.3 (M+H). Calc'd for C₈H₁₂N₂OS - 184.26

Preparation DL: 2-(5-tert-Butyl-oxazol-2-yl)-thiazole-4-carboxylic acid ethyl ester

15 In a manner similar to that described in preparation BC, the title compound was isolated as a white solid. MS m/z: 281.2 (M+H). Calc'd for C₁₃H₁₆N₂O₃S - 280.34

20 Preparation DM: 2-(5-tert-Butyl-oxazol-2-yl)-thiazole-4-carboxylic acid

In a manner similar to that described in preparation BD, the title compound was isolated as a white solid. MS m/z: 253.3 (M+H). Calc'd for C₁₁H₁₂N₂O₃S - 252.29

25 Preparation DN: 2-(5-tert-Butyl-oxazol-2-yl)-thiazole-4-carbonyl azide

In a manner similar to that described in preparation BE, the title compound was isolated as an off-white solid. 30 MS m/z: 278.2 (M+H)⁺. Calc'd for C₁₁H₁₁N₅O₂S - 277.30

Preparation DO: 2-Thiophen-2-yl-thiazole-4-carboxylic acid ethyl ester

The mixture of 2-bromo-thiazole-4-carboxylic acid ethyl ester (0.965 g, 4.09 mmol), 2-thiopheneboronic acid (0.52 g, 4.09 mmol), $\text{Pd}(\text{PPh}_3)_4$ (0.24 g, 0.20 mmol) in 6.2 mL of 2M Na_2CO_3 (aq) and 25 mL of ethylene glycol dimethyl ether was heated at reflux for 16 h, cooled to RT, diluted with H_2O (25 mL), and extracted with EtOAc (30 mL x 3). The combined organic portions were washed with brine, dried with Na_2SO_4 , and filtered. Removal of the solvents afforded a light yellowish oil which was purified by flash column chromatography (5% to 10% of EtOAc in hexanes). The desired compound was obtained as a pale solid. MS m/z: 239.9 ($\text{M}+\text{H}$). Calc'd for $\text{C}_{10}\text{H}_9\text{NO}_2\text{S}_2$ - 239.32.

Preparation DP: 2-(Thiophene-2-sulfonylmethyl)-thiazole-4-carboxylic acid ethyl ester

In a manner similar to that described in preparation BC, the title compound was isolated as a light yellowish viscous oil. MS m/z: 318.1 ($\text{M}+\text{H}$). Calc'd for $\text{C}_{11}\text{H}_{11}\text{NO}_4\text{S}_3$ - 317.41.

Preparation DQ: 2-(Thiophene-2-sulfonylmethyl)-thiazole-4-carboxylic acid

In a manner similar to that described in preparation BD, the title compound was isolated as a white solid. MS m/z: 290.0 ($\text{M}+\text{H}$). Calc'd for $\text{C}_9\text{H}_7\text{NO}_4\text{S}_3$ - 289.35.

Preparation DR: 2-(Thiophene-2-sulfonylmethyl)-thiazole-4-carbonyl azide

In a manner similar to that described in preparation BE, the title compound was isolated as a tan solid. MS m/z: 315.1 ($\text{M}+\text{H}$). Calc'd for $\text{C}_9\text{H}_6\text{N}_4\text{O}_3\text{S}_3$ - 314.37.

Preparation DS: 6-(1-Methyl-piperidin-4-yloxy)-pyridin-2-ylamine

In a manner similar to that described in Preparation EM, the title compound was isolated as a white solid. MS m/z: 208.1 (M+H). Calc'd for C₁₁H₁₇N₃O- 207.27.

5 **Preparation DT: 4-(6-Amino-pyridin-2-yloxyethyl)-piperidine-1-carboxylic acid tert-butyl ester**

In a manner similar to that described in Preparation EM, the title compound was isolated as a white solid. MS m/z: 308.2 (M+H). Calc'd for C₁₆H₂₅N₃O₃- 307.39.

10

Preparation DU: D-2-Hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of D-prolinol (8 g, 79.2 mmol) and CH₂Cl₂ (150 mL) was added (Boc)₂O (19 g, 87.1 mmol) and 150 mL of sat'd NaHCO₃. The reaction was stirred at RT for 15 h. Extraction with CH₂Cl₂, washing with brine, drying (MgSO₄) and concentration *in vacuo* gave D-2-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester as a white solid. MS m/z: 202.3 (M+H). Calc'd for C₁₀H₁₉NO₃ - 201.26.

Preparation DV: 2-(6-Bromo-pyridin-2-yloxyethyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of D-2-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (15.9 g, 79.1 mmol) and dry DMF (250 mL) was added NaH (3.8 g, 94.9 mmol, 60% in mineral oil). Stirred at RT for 15 h, then added 2,6-dibromopyridine. Heated to 90°C for 2 h. Cooled and extracted with EtOAc. Washed organic layer with H₂O and brine, dried (MgSO₄) and concentrated *in vacuo* to give an orange oil. Purified by silica flash chromatography (10% EtOAc/hexane) to give the desired compound as a clear-colorless oil. MS m/z: 358.2 (M+H). Calc'd for C₁₅H₂₁BrN₂O₃ - 357.24.

35

Preparation DW: 2-(6-Amino-pyridin-2-yloxyethyl)-
pyrrolidin -1-carboxylic acid tert-butyl ster

In a manner similar to Preparation BW to give 2-(6-amino-pyridin-2-yloxyethyl)-pyrrolidine-1-carboxylic acid 5 tert-butyl ester as a viscous green oil. MS m/z : 294.3 (M+H). Calc'd for $C_{15}H_{23}N_3O_3$ - 293.36.

Preparation DX: 2-Bromo-6-(tetrahydro-furan-3-yloxy)-
pyridine

10 To a solution of (S)-(+)-3-hydroxy-tetrahydrofuran (0.34 mL, 4.2 mmol) and dry THF (20 mL) was added NaH (0.17 g, 4.2 mmol, 60%) under N_2 at RT. After 5 min, added 2,6-dibromopyridine. Stirred at RT for 4 h. Quenched with H_2O and extracted with EtOAc. Washed organic layer with 15 saturated NH_4Cl , brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 2-bromo-6-(tetrahydro-furan-3-yloxy)-pyridine as a clear, colorless oil. MS m/z : 245.2 (M+H). Calc'd for $C_9H_{10}BrNO_2$ - 244.09.

20 Preparation DY: 2-Bromo-6-(tetrahydro-furan-2-ylmethoxy)-
pyridine
In a manner similar to preparation DX from tetrahydro-furfuryl alcohol to give 2-bromo-6-(tetrahydro-furan-2-ylmethoxy)-pyridine as a white solid. MS m/z : 259.2 (M+H). Calc'd for $C_{10}H_{12}BrNO_2$ 258.11.

Preparation DZ: 2-Bromo-6-(tetrahydro-furan-2-ylmethoxy)-
pyridine

In a manner similar to preparation DX from tetrahydro-30 3-furan methanol to give 2-bromo-6-(tetrahydro-furan-2-ylmethoxy)-pyridine as a white solid. MS m/z : 259.2 (M+H). Calc'd for $C_{10}H_{12}BrNO_2$ 258.11

35 Preparation EA: 6-(Tetrahydro-furan-3-yloxy)-pyridin-2-
ylamine

In a manner similar to preparation BW and 2-bromo-6-(tetrahydrofuran-3-yloxy)-pyridine to give 6-(tetrahydrofuran-3-yloxy)-pyridin-2-ylamine as a dark-green oil. MS m/z : 181.0 (M+H). Calc'd for $C_9H_{12}N_2O_2$ - 180.20.

5

Preparation EB: 6-(Tetrahydro-furan-2-ylmethoxy)-pyridin-2-ylamine

In a manner similar to preparation BW from 2-bromo-6-(tetrahydro-furan-2-ylmethoxy)-pyridine to give 6-(tetrahydro-furan-3-yloxy)-pyridin-2-ylamine as a dark-green oil. MS m/z : 384.3 (M+H). Calc'd for $C_{10}H_{14}N_2O_2$ 194.23.

10 15 **Preparation EC: 6-(Tetrahydro-furan-3-ylmethoxy)-pyridin-2-ylamine**

In a manner similar to preparation BW from 2-bromo-6-(tetrahydro-furan-2-ylmethoxy)-pyridine to give 6-(tetrahydro-furan-3-ylmethoxy)-pyridin-2-ylamine as a yellow oil. MS m/z : 195.0 (M+H). Calc'd for $C_{10}H_{14}N_2O_2$ 194.23.

20

Preparation ED: 6-Bromo-1'-methyl-2',3',5',6'-tetrahydro-1'H-[2,4']bipyridinyl-4'-ol

To a solution of 1.07 M n-BuLi (36.4 mL) and dry THF (200 mL) chilled to -70°C under a blanket of N_2 was added 2,6-dibromopyridine (10 g, 38.9 mmol) in 50 mL of dry THF slowly to maintain a temperature less than -69°C. Stirred at -70°C for 20 min. Added 4-methylpiperidone (4.8 mL, 38.9 mmol) and stirred the mixture at -70°C for 1 h. Quenched with saturated $NaHCO_3$ and extracted with EtOAc. Washed the organic layer with brine, dried ($MgSO_4$) and concentrated in vacuo to give 6-bromo-1'-methyl-2',3',5',6'-tetrahydro-1'H-[2,4']bipyridinyl-4'-ol as a light-yellow solid. MS m/z : 272.3 (M+H). Calc'd for $C_{11}H_{15}BrN_2O$ - 271.15.

30 35 **Preparation EE: 6-Bromo-1'-methyl-1',2',3',6'-tetrahydro-[2,4']bipyridinyl**

To a 150 mL flask containing 6-bromo-1'-methyl-2',3',5',6'-tetrahydro-1'H-[2,4']bipyridinyl-4'-ol (5 g, 18.5 mmol) was added conc. H_2SO_4 (50 mL). Heated to 100°C for 18 h. Cooled and poured onto ice carefully.

5 Neutralized with 5 N NaOH and extracted with EtOAc. Washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. Diluted residue with EtOAc and filtered. Concentrated filtrate *in vacuo* to give 6-bromo-1'-methyl-1',2',3',6'-tetrahydro-[2,4']bipyridinyl as an orange oil. MS *m/z*: 10 254.2 (M+H). Calc'd for $C_{11}H_{13}BrN_2$ 253.14.

Preparation EF: 1'-Methyl-1',2,3',6'-tetrahydro-[2,4']bipyridinyl-6-ylamine

In a manner similar to preparation xxx from 6-bromo-1'-methyl-1',2',3',6'-tetrahydro-[2,4']bipyridinyl to give 1'-methyl-1',2,3',6'-tetrahydro-[2,4']bipyridinyl-6-ylamine as a yellow oil. MS *m/z*: 190.0 (M+H). Calc'd for $C_{11}H_{15}N_3$ 189.26.

20 **Preparation EG: 1'-Methyl-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl-6-ylamine**

A solution of 1'-methyl-1',2,3',6'-tetrahydro-[2,4']bipyridinyl-6-ylamine (1.1 g, 5.8 mmol) and EtOH (30 mL) was hydrogenated over 20% $Pd(OH)_2/C$ (0.3 g) at 40 psi and RT. After 16 h, the mixture was filtered through Celite® and concentrated *in vacuo* to give the desired compound as a yellow solid. MS *m/z*: 192.1 (M+H). Calc'd for $C_{11}H_{17}N_3$ - 191.27.

30 **Preparation EH: 6-Bromo-4-hydroxy-3',4',5',6'-tetrahydro-2'H-[2,4']bipyridinyl-1'-carboxylic acid tert-butyl ester**

In a manner similar to Preparation ED from N-Boc-piperidone to give the desired compound as a yellow oil. MS *m/z*: 358.0 (M+H). Calc'd for $C_{15}H_{21}BrN_2O_3$ 357.24.

Preparation EI: 6-Bromo-1',2',3',6'-tetrahydro-[2,4']bipyridinyl

In a manner similar to Preparation EE from 6-bromo-4-hydroxy-3',4',5',6'-tetrahydro-2'H-[2,4']bipyridinyl-1'-carboxylic acid tert-butyl ester to give the desired compound as a yellow solid. MS *m/z*: 240.1 (M+H). Calc'd for C₁₀H₁₁BrN₂ 239.11.

10 Preparation EJ: 6-Bromo-3',6'-dihydro-2'H-[2,4']bipyridinyl-1'-carboxylic acid tert-butyl ester

To a solution of 6-bromo-1',2',3',6'-tetrahydro-[2,4']bipyridinyl (4.3 g, 17.8 mmol) and CH₂Cl₂ (100 mL) was added saturated NaHCO₃ (100 mL) and (Boc)₂O (3.8 g, 17.8 mmol). Stirred at RT for 18 h. Washed organic layer with brine then dried (MgSO₄) and concentrated *in vacuo* to give the desired compound as a light-yellow oil. MS *m/z*: 338.9 (M-H). Calc'd for C₁₅H₁₉BrN₂O₂ 339.23.

20 Preparation EK: 6-Amino-3',4',5',6'-tetrahydro-2'H-[2,4']bipyridinyl-1'-carboxylic acid tert-butyl ester

In a manner similar to Preparation EG from 6-amino-3',6'-dihydro-2'H-[2,4']bipyridinyl-1'-carboxylic acid tert-butyl ester to give the desired compound as a yellow oil. MS *m/z*: 278.3 (M+H). Calc'd for C₁₅H₂₃N₃O₂ 277.36.

25 Preparation EL: 6-Amino-3',6'-dihydro-2'H-[2,4']bipyridinyl-1'-carboxylic acid tert-butyl ester

In a manner similar to Preparation BW from 6-bromo-3',6'-dihydro-2'H-[2,4']bipyridinyl-1'-carboxylic acid tert-butyl ester to give the desired compound as a yellow oil. MS *m/z*: 275.6 (M+H). Calc'd for C₁₅H₂₁N₃O₂ 275.35.

Preparation EM: 3-(6-Bromo-pyridin-2-ylamino)-propan-1-ol

A solution of 2,6-dibromopyridine (10 g, 42 mmol) and 35 3-aminopropanol (3.5 mL, 46 mmol) in THF (60 mL) was stirred

at reflux for 48 h. The reaction mixture was diluted with EtOAc and washed with H₂O and brine, dried (MgSO₄) and concentrated *in vacuo* to give 3-(6-bromo-pyridin-2-ylamino)-propan-1-ol as a light-yellow oil which crystallized on standing at RT to a white solid. MS *m/z*: 232.0 (M+H).
5 Calc'd for C₈H₁₁BrN₂O 231.09.

Preparation EN: (6-Bromo-pyridin-2-yl)-[3-(tetrahydro-pyran-2-yloxy)-propyl]-amine

10 A solution of 3-(6-bromo-pyridin-2-ylamino)-propan-1-ol (4.2 g, 18 mmol), 3,4-dihydro-2H-pyran (1.6 mL, 18 mmol), TsOH (0.34 g, 1.8 mmol) and CH₂Cl₂ (100 mL) were stirred at RT. After 15 h, the reaction was quenched with saturated NaHCO₃ and extracted with EtOAc. The organic layer was washed with brine, dried (MgSO₄) and concentrated *in vacuo* to give the desired compound as a pale-yellow oil. MS *m/z*: 316.0 (M+H). Calc'd for C₁₃H₁₉BrN₂O₂ 315.21.

Preparation EO: N-[3-(Tetrahydro-pyran-2-yloxy)-propyl]-pyridine-2,6-diamine

20 In a manner similar to Preparation BW from (6-bromo-pyridin-2-yl)-[3-(tetrahydro-pyran-2-yloxy)-propyl]-amine to give the desired compound as green oil. MS *m/z*: 252.0 (M+H). Calc'd for C₁₃H₂₁N₃O₂ 251.32.

Preparation EP: 1-(2-Pyridin-4-yl-thiazol-4-yl)-3-[6-[3-(tetrahydro-pyran-2-yloxy)-propylamino]-pyridin-2-yl]-urea

25 In a manner similar to Example 234, 2-(4-pyridinyl)-4-thiazolcarbonylazide and N-[3-(tetrahydro-pyran-2-yloxy)-propyl]-pyridine-2,6-diamine were heated together in toluene to give the desired compound as a yellow solid. MS *m/z*: 452.9 (M-H). Calc'd for C₂₂H₂₆N₆O₃S 454.55.

Preparation EQ: 1-(2-Bromo-thiazol-4-yl)-3-[6-[3-(tetrahydro-pyran-2-yloxy)-propylamino]-pyridin-2-yl]-urea

In a manner similar to Example 234, 2-bromo-thiazole-4-carbonyl azide and N-[3-(tetrahydro-pyran-2-yloxy)-propyl]-pyridine-2,6-diamine were heated together in toluene to give the desired compound as a yellow solid. MS *m/z*: 5 457.3 (M-H). Calc'd for $C_{17}H_{22}BrN_5O_3S$ 456.36.

Preparation ER: 1-Acetyl-1H-indazole-5-carbonitrile

In a manner similar to that described by J. Sun, et al, J.O.C., 1997, p. 5627 from 4-amino-3-methylbenzo-nitrile, acetic anhydride, KOAc and CHCl₃ to give 1-acetyl-1H-indazole-5-carbonitrile as a yellow solid. MS *m/z*: 10 186.0 (M+H). Calc'd for $C_{10}H_7N_3O$ 185.18.

Preparation ES: 1-Acetyl-1H-indazole-5-carbothioic acid

15 **amide**

To a solution of 1-acetyl-1H-indazole-5-carbonitrile (1.1 g, 6 mmol), Et₃N (2.5 mL, 17.8 mmol) and THF (20 mL) was bubbled in H₂S gas over 10 min. Stirred at 0°C for 24 h. Concentrated *in vacuo* to give a yellow solid which was 20 triturated with CH₂Cl₂ and filtered insoluble solid to give 1-acetyl-1H-indazole-5-carbothioic acid amide as a yellow solid. MS *m/z*: 220.0 (M+H). Calc'd for $C_{10}H_9N_3OS$ 219.26.

25 **Preparation ET: 2-(1-Acetyl-1H-indazol-5-yl)-thiazole-4-carboxylic acid ethyl ester**

In a manner similar to Preparation CV from 1-acetyl-1H-indazole-5-carbothioic acid amide to give 2-(1-acetyl-1H-indazol-5-yl)-thiazole-4-carboxylic acid ethyl ester as a white solid. MS *m/z*: 316.2 (M+H). Calc'd for $C_{15}H_{13}N_3O_3S$ 30 315.35.

Preparation EU: 2-(1-Acetyl-1H-indazol-5-yl)-thiazole-4-carboxylic acid

In a manner similar to Preparation CW from 2-(1-acetyl-1H-indazol-5-yl)-thiazole-4-carboxylic acid ethyl ester to give 2-(1-acetyl-1H-indazol-5-yl)-thiazole-4-carboxylic acid as a yellow solid following re-protection 5 with Ac₂O, Et₃N, and THF. MS m/z: 286.1 (M-H). Calc'd for C₁₃H₉N₃O₃S 287.29.

Preparation EV: 2-(1-Acetyl-1H-indazol-5-yl)-thiazole-4-carbonyl azide

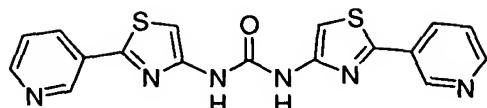
10 In a manner similar to Preparation CX from 2-(1-acetyl-1H-indazol-5-yl)-thiazole-4-carboxylic acid to give 2-(1-acetyl-1H-indazol-5-yl)-thiazole-4-carbonyl azide as a white solid. MS m/z: (M+H). Calc'd for C₁₃H₈N₆O₂S 312.31.

15 **Preparation EW: 6-(1-Piperidin-1-yl-ethyl)-pyridin-2-ylamine**

In a manner similar to that described in Preparation BW, 2-bromo-6-(1-piperidin-1-yl-ethyl)-pyridine (370 mg, 1.37 mmol) was heated with NH₄OH (18 mL), IpOH (10 mL), and Cu (30 mg) in sealed tube to give a brown oil. MS m/z: 20 206.1 (M+H). Calc'd. for C₁₂H₁₉N₃ - 205.16.

Preparation EX: (6-Amino-pyridin-2-ylmethyl)-isopropyl-carbamic acid tert-butyl ester

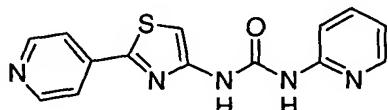
Prepared in a manner similar to preparation BW to give 25 a pale yellow solid. EI-MS m/z 266.3 (M+H). Calc'd for C₁₄H₂₃N₃O₂: 265.18.

Example 1

5

N,N'-bis [2-(3-Pyridinyl)-4-thiazolyl] urea

To a 50 mL round bottomed flask were added 0.106 g (0.458 mmol) of 2-(3-pyridinyl)-4-thiazolyl-carbonylazide, 10 toluene (10 mL) and 5 drops of H₂O. The mixture was heated at 95°C for 4 h then cooled to RT. The precipitate that formed was filtered, washed with a minimum amount of toluene and dried under high vacuum to give the product as a pale yellow solid. MS *m/z*: 381.5 (M+H). Calc'd. for C₁₇H₁₂N₆OS₂ - 15 380.453.

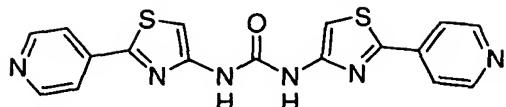
Example 2

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N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-pyridinylurea

To a solution of 2-(4-pyridinyl)-4-thiazolyl-carbonylazide (60 mg, 0.260 mmol) in 10 mL toluene was added 25 2-aminopyridine (35 mg, 0.372 mmol). The mixture was heated at 95 °C for 18 h then cooled to RT and filtered. The precipitate was washed with toluene (3mL) and dried under high vacuum to give the product as a pale yellow solid. MS *m/z*: 298.5 (M+H). Calc'd. for C₁₄H₁₁N₅OS - 297.341.

30

Example 3

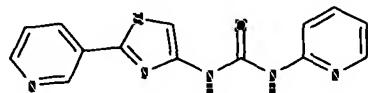
5

N,N'-bis [2-(4-Pyridinyl)-4-thiazolyl] urea

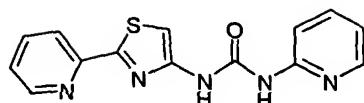
In a manner similar to that described in Example 2, 2-(4-pyridinyl)-4-thiazolylcarbonylazide (130 mg, 0.562 mmol) was heated in toluene (10 mL) containing 4 drops of H₂O to 10 give the product as a pale yellow solid. MS m/z: 381.5 (M+H). Calc'd. for C₁₇H₁₂N₆OS₂ - 380.453.

Example 4

15

**N-[2-(3-Pyridinyl)-4-thiazolyl]-N'-2-pyridinylurea**

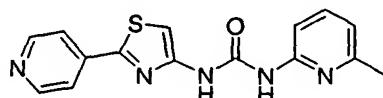
In a manner similar to that described in Example 2, 2-(3-pyridinyl)-4-thiazolylcarbonylazide (48 mg, 0.208 mmol) and 2-aminopyridine (24 mg, 0.255 mmol) were heated in toluene (10 mL) to give the product as a pale yellow solid. MS m/z: 298.4 (M+H). Calc'd. for C₁₄H₁₁N₅OS - 297.341.

Example 5

5

N-[2-(2-Pyridinyl)-4-thiazolyl]-N'-2-pyridinylurea

2-(2-Pyridinyl)-4-thiazolylcarbonylazide (200 mg, 0.87 mmol) and 2-aminopyridine (318 mg, 2.6 mmol) were heated in toluene (10 mL) at 100°C for 14 h. After cooling to RT, the solids were collected by filtration and washed first with toluene (2x20 mL) followed by Et₂O (2x10mL) and cold EtOAc (3x5 mL). The solid was recrystallized from EtOAc to afford the product as an off-white solid: m.p. 233-235°C. MS *m/z*: 298 (M+H). Calc'd for C₁₄H₁₁N₅OS 297.341.

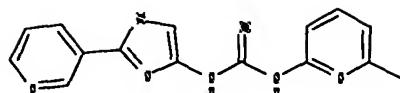
Example 6

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N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-(6-methylpyridinyl)urea

In a manner similar to that described in Example 2, 2-(4-pyridinyl)-4-thiazolylcarbonylazide (69 mg, 0.298 mmol) and 2-amino-6-methylpyridine (101 mg, 0.934 mmol) were heated in toluene (10 mL) to give the product as a pale yellow solid. MS *m/z*: 312.5 (M+H). Calc'd. for C₁₅H₁₃N₅OS - 311.368.

30

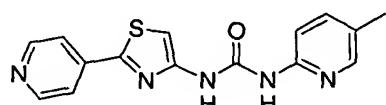
Example 7

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N-[2-(3-Pyridinyl)-4-thiazolyl]-N'-2-(6-methylpyridinyl)urea

In a manner similar to that described in Example 2, 2-(3-pyridinyl)-4-thiazolylcarbonylazide (78 mg, 0.337 mmol) and 2-amino-6-methylpyridine (101 mg, 0.934 mmol) were heated in toluene (10 mL) to give the product as a pale yellow solid. MS m/z : 312.2 (M+H). Calc'd. for $C_{15}H_{13}N_5OS$ - 311.368.

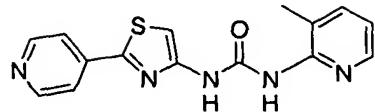
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Example 8

20

N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-(5-methylpyridinyl)urea

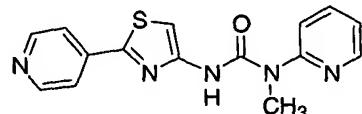
In a manner similar to that described in Example 2, 2-(4-pyridinyl)-4-thiazolylcarbonylazide (72 mg, 0.311 mmol) and 2-amino-5-methylpyridine (106 mg, 0.981 mmol) were heated in toluene (10 mL) to give the product as a pale yellow solid. MS m/z : 312.5 (M+H). Calc'd. for $C_{15}H_{13}N_5OS$ - 311.368.

Example 95 **N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-(3-methylpyridinyl)urea**

In a manner similar to that described in Example 2, 2-(4-pyridinyl)-4-thiazolylcarbonylazide (135 mg, 0.584 mmol) and 2-amino-3-methylpyridine (200 mg, 1.98 mmol) were heated 10 in toluene (10 mL) to give the product as a pale yellow solid. MS *m/z*: 312.4 (M+H). Calc'd. for C₁₅H₁₃N₅OS ~ 311.368.

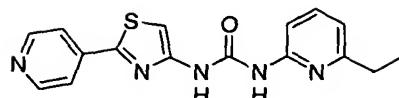
Example 10

15

**N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-pyridinyl-N'-methylurea**

20 In a manner similar to that described in Example 2, 2-(4-pyridinyl)-4-thiazolylcarbonylazide (71 mg, 0.310 mmol) and 2-methylaminopyridine (210 mg, 1.94 mmol) were heated in toluene (7 mL) to give the product as pale yellow crystals. MS *m/z*: 312.5 (M+H). Calc'd. for C₁₅H₁₃N₅OS ~ 311.368.

25

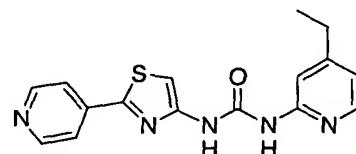
Example 11

5

N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-(6-ethylpyridinyl)urea

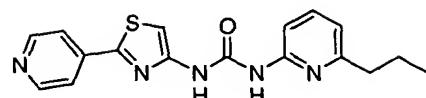
In a manner similar to that described in Example 2, 2-(4-pyridinyl)-4-thiazolylcarbonylazide (75 mg, 0.324 mmol) and 2-amino-6-ethylpyridine (200 mg, 1.63 mmol) were heated in toluene (8 mL) to give the product as a pale yellow solid. MS *m/z*: 326.5 (M+H). Calc'd. for C₁₆H₁₅N₅OS - 325.395.

15

Example 12

20

In a manner similar to that described in Example 2, 2-(4-pyridinyl)-4-thiazolylcarbonylazide (82 mg, 0.355 mmol) and 2-amino-4-ethylpyridine (106 mg, 0.867 mmol) were heated in toluene (10 mL) to give the product as a pale yellow solid. MS *m/z*: 326.5 (M+H). Calc'd. for C₁₆H₁₅N₅OS - 325.395.

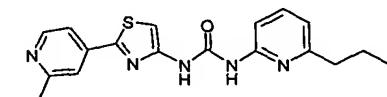
Example 13

5

N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-(6-propylpyridinyl)urea

In a manner similar to that described in Example 3, 2-(4-pyridinyl)-4-thiazolylcarbonylazide (89 mg, 0.385 mmol) and 2-amino-6-(n-propyl)pyridine (171 mg, 1.25 mmol) were heated in toluene (10 mL) to give the product as a pale yellow solid. MS *m/z*: 339.4 (M+H). Calc'd. for C₁₇H₁₇N₅OS - 339.422.

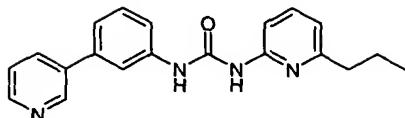
15

Example 14

20

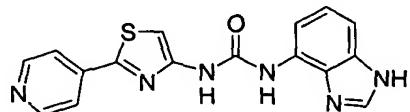
N-[2-(2-Ethyl-4-pyridinyl)-4-thiazolyl]-N'-2-(6-propylpyridinyl)urea

In a manner similar to that described in Example 6, 2-(4-(2-ethyl)-pyridinyl)-4-thiazolylcarbonylazide (460 mg, 1.77 mmol) and 2-amino-6-(n-propyl)pyridine (483 mg, 3.55 mmol) were heated in toluene (20 mL) at 100°C for 14 h. After cooling to RT, the solids were collected by filtration and washed first with toluene (2 x 20 mL) followed by EtOAc:Et₂O (4:1) (4 x 20 mL) to give the product as an off-white solid: m.p. 204-206°C. MS *m/z*: 368 (M+H). Calc'd. for C₁₉H₂₁N₅OS - 367.476.

Example 155 **N- [3- (3-Pyridinyl)phenyl]-N'-2-(6-propylpyridinyl)urea**

To a suspended anhydrous solution of 3-pyridylaniline (90 mg, 0.53 mmol) in dry toluene (4 mL) was added phosgene (0.36 mL, 0.69 mmol, 20% in toluene) followed by DIEA (0.20 mL, 1.05 mmol) under an atmosphere of argon. After stirring for 0.5 h at RT, 2-amino-6-n-propylpyridine (72 mg, 0.53 mmol) in dry toluene (4 mL) was added dropwise into the mixture. The resulting mixture was stirred at RT for 18 h. The organic solvent was removed under vacuum. The residue was purified by chromatography on flash silica gel using 2% MeOH/CH₂Cl₂ as eluant to obtain the final urea as an off-white solid. MS *m/z* :333.4 (M+H). Calc'd. for C₂₀H₂₀N₄O - 332.405.

20

Example 1625 **N- [2- (4-Pyridinyl)-4-thiazolyl]-N'-4-benzimidazolylurea**

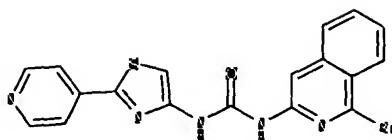
25

In a manner similar to that described in Example 2, 2-(4-pyridinyl)-4-thiazolylcarbonylazide (32 mg, 0.138 mmol) and 4-aminobenzimidazole (32 mg, 0.240 mmol) were heated in toluene (8 mL). The crude product was recrystallized with CH₃CN:MeOH (~10:1) to give the product as a pale brown

solid. MS m/z : 337.5 (M+H). Calc'd. for $C_{16}H_{12}N_6OS$ - 336.378.

Example 17

5



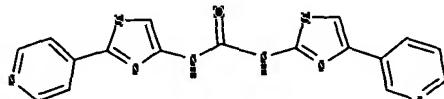
N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-3-(1-bromoisoquinolinyl)urea

10

In a manner similar to that described in Example 2, 2-(4-pyridinyl)-4-thiazolylcarbonylazide (61 mg, 0.264 mmol) and 3-amino-1-bromo-isoquinoline (120 mg, 0.538 mmol) were heated in toluene (10 mL) to give the product as a pale yellow solid. MS m/z : 427.2 (M+H). Calc'd. for $C_{18}H_{12}BrN_5OS$ - 426.297.

Example 18

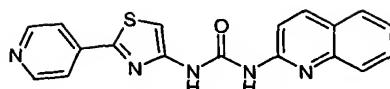
20



N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-(4-(3-pyridinyl)-2-thiazolyl) urea

25

In a manner similar to that described in Example 2, 2-(4-pyridinyl)-4-thiazolylcarbonylazide (36 mg, 0.298 mmol) and 2-amino-4-(3-pyridyl)-thiazole (29 mg, 163 mmol) were heated in toluene (10 mL) to give the product as a pale yellow solid. MS m/z : 381.5 (M+H). Calc. for $C_{17}H_{12}N_6OS_2$ - 380.453.

Example 19

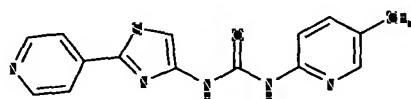
5

N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-quinolinylurea

In a manner similar to that described in Example 2, 2-(4-pyridinyl)-4-thiazolylcarbonylazide (38 mg, 0.164 mmol) and 2-aminoquinoline (53 mg, 0.370 mmol) were heated in toluene (10 mL) to give the product as a pale yellow solid. MS *m/z*: 348.4 (M+H). Calc. for C₁₈H₁₃N₅OS ~ 347.401.

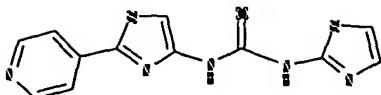
Example 20

15

**N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-(5-trifluoromethylpyridinyl)urea**

20

In a manner similar to that described in Example 2, 2-(4-pyridinyl)-4-thiazolylcarbonylazide (40 mg, 0.173 mmol) and 2-amino-5-trifluoromethylpyridine (165 mg, 1.02 mmol) were heated in 10 mL toluene to give the product as a pale yellow solid. MS *m/z*: 366.3 (M+H). Calc'd. for C₁₅H₁₀F₃N₅OS ~ 365.339.

Example 21

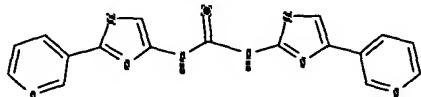
5

N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-thiazolylurea

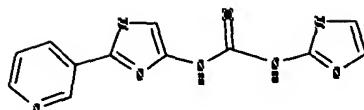
In a manner similar to that described in Example 2, 2-(4-pyridinyl)-4-thiazolylcarbonylazide (70 mg, 0.303 mmol) and 2-aminothiazole (38 mg, 0.38 mmol) were heated in toluene (12 mL) to give the product as a pale yellow solid. MS *m/z*: 304.4 (M+H). Calc'd. for C₁₂H₉N₅OS₂ - 303.366.

Example 22

15

**N-[2-(3-Pyridinyl)-4-thiazolyl]-N'-[4-(3-pyridinyl)-2-thiazolyl] urea**

In a manner similar to that described in Example 2, 2-(3-pyridinyl)-4-thiazolylcarbonylazide (36 mg, 0.156 mmol) and 2-amino-4-(3-pyridinyl)thiazole (30 mg, 0.169 mmol) were heated in toluene (8 mL) to give the product as a pale yellow solid. MS *m/z*: 381.5 (M+H). Calc'd. for C₁₇H₁₂N₆OS₂ - 380.453.

Example 23

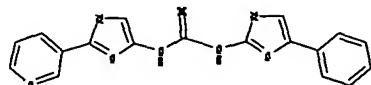
5

N-[2-(3-Pyridinyl)-4-thiazolyl]-N'-2-thiazolylurea

In a manner similar to that described in Example 2, 2-(3-pyridinyl)-4-thiazolylcarbonylazide (59 mg, 0.255 mmol) and 2-aminothiazole (27 mg, 268 mmol) were heated in toluene (10 mL) to give the product as a pale yellow solid. MS *m/z*: 304.3 (M+H). Calc'd. for $C_{12}H_9N_5OS_2$ - 303.366.

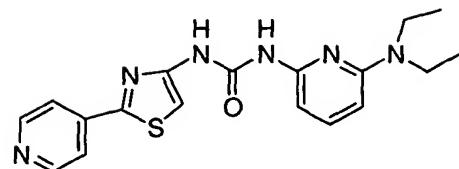
Example 24

15

**N-[2-(3-Pyridinyl)-4-thiazolyl]-N'-[4-phenyl-2-thiazolyl]urea**

20

In a manner similar to that described in Example 2, 2-(3-pyridinyl)-4-thiazolylcarbonylazide (49 mg, 0.211 mmol) and 2-amino-4-phenylthiazole (39 mg, 0.218 mmol) were heated in toluene (10 mL) to give the product as a pale yellow solid. MS *m/z*: 380.5 (M+H). Calc'd. for $C_{18}H_{13}N_5OS_2$ - 379.465.

Example 25

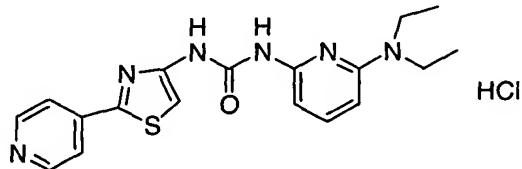
5

N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-[6-(N'',N''-diethylamino)pyridinyl]urea

A mixture of 2-(4-pyridinyl)-4-thiazolyl-carbonylazide (100 mg, 0.43 mmol) and 2-amino-6-(N,N-diethylamino)pyridine (150 mg, 0.91 mmol) in toluene (3 mL) was heated at 70°C for 1 h, and then at 80°C for 5 h. After the mixture was cooled to RT the solvent was removed in vacuo and the crude product was purified by chromatography on silica gel (1:10 MeOH(NH₃)/CH₂Cl₂) to give N-[2-(4-pyridinyl)-4-thiazolyl]-N'-2-[6-(N'',N''-diethylamino)pyridinyl]urea. MS m/z: 369 (M+1). Calc'd. for C₁₈H₂₀N₆OS - 368.463.

Example 26

20



N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-[6-(N'',N''-diethylamino)pyridinyl]urea hydrochloride

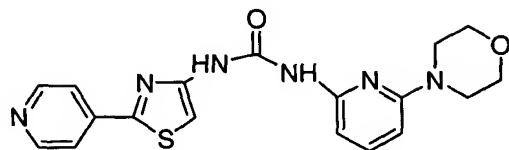
25

N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-[6-(N'',N''-diethylamino)pyridinyl]urea (Example 25) was dissolved in 5 ml of MeOH/CH₂Cl₂ (1:1) and (1M) HCl (8 mL) in Et₂O solution

was added. The solvents were removed *in vacuo* to afford the title salt as a yellow solid.

Example 27

5



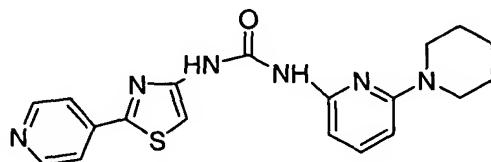
N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-[6-(4-morpholinyl)pyridinyl]urea

10

A mixture of 2-(4-pyridinyl)-4-thiazolyl-carbonylazide (100 mg, 0.43 mmol) and 2-amino-6-(4-morpholinyl)pyridine (150 mg, 0.84 mmol) in toluene (5 mL) was heated at 80°C for 5 h. After the mixture was cooled to 15 RT the solvent was removed *in vacuo* and the crude product was purified by chromatography on silica gel (1:10 MeOH(NH₃)/CH₂Cl₂) to afford the title compound as a light yellow solid. MS m/z: 383 (M+1). Calc'd. for C₁₈H₁₈N₆O₂S - 382.446.

20

Example 28



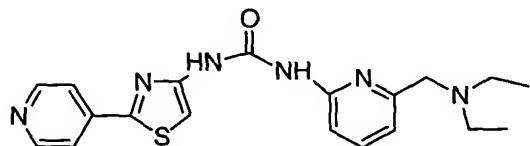
25

N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-[6-(1-piperidinyl)pyridinyl]urea

A mixture of 2-(4-pyridinyl)-4-thiazolyl-carbonylazide (100 mg, 0.43 mmol) and 2-amino-6-(1-piperidinyl)pyridine

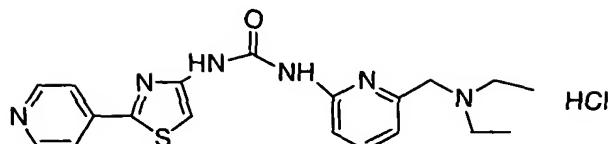
(100 mg, 0.56 mmol) in toluene (3 mL) was heated at 80°C for 4 h. After cooling to RT, H₂O was added and the mixture was extracted with EtOAc (3x80 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and 5 concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (1:20 MeOH/CH₂Cl₂) to afford the title compound as a light yellow solid. MS m/z: 381 (M+1). Calc'd for C₁₉H₂₀N₆OS - 380.475.

10

Example 29

A mixture of 2-(4-pyridinyl)-4-thiazolyl-carbonylazide (100 mg, 0.43 mmol) and 2-amino-6-(N,N-diethylaminomethyl)pyridine (150 mg, 0.84 mmol) in toluene 20 (5 mL) was heated at 80°C for 5 h. After the mixture was cooled to RT the solvent was removed *in vacuo* and the crude product was purified by chromatography on silica gel (1:10 MeOH(NH₃)/CH₂Cl₂) to give the base. MS m/z: 383 (M+1). Calc'd. for C₁₉H₂₂N₆OS - 382.49.

25

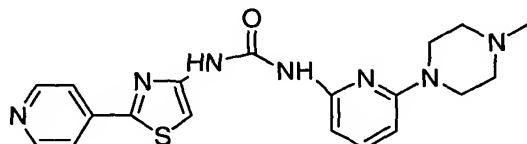
Example 30

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N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-[6-(N'',N''-diethylaminomethylamino)pyridinyl]urea hydrochloride

10 N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-[6-(N'',N''-diethylaminomethylamino)pyridinyl]urea (Example 29) was dissolved in 5 ml of MeOH/CH₂Cl₂ (1:1) and 1M HCl (8 mL) in Et₂O solution was added. The solvents were removed *in vacuo* to afford the title salt as a yellow solid.

15

Example 31

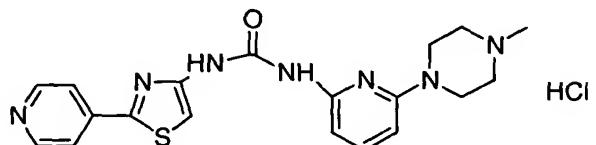
20 **N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-[6-(1-methyl-4-piperazinyl)pyridinyl]urea**

25 A mixture of 2-(4-pyridinyl)-4-thiazolyl-carbonylazide (100 mg, 0.43 mmol) and 2-amino-6-(1-(4-methyl)piperazinyl)pyridine (100 mg, 5.21 mmol) in toluene (5 mL) was heated at 80°C for 5 h. After the mixture was cooled to RT the solvent was removed *in vacuo*. The crude product was purified by chromatography on silica gel (1:10 MeOH(NH₃) / CH₂Cl₂) to give N-[2-(4-pyridinyl)-4-thiazolyl]-N'-

2-[6-(1-methyl-4-piperazinyl)pyridinyl]urea. m.p. 251-253°C.
MS *m/z*: 396 (M+1). Calc'd. for C₁₉H₂₂N₆OS - 395.489.

Example 32

5

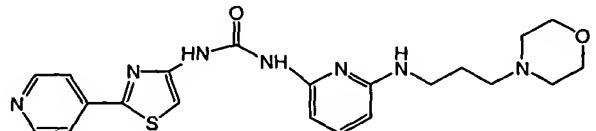


N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-[6-(1-methyl-4-piperazinyl)pyridinyl]urea hydrochloride

10

N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-[6-(1-methyl-4-piperazinyl)pyridinyl]urea (Example 31) was dissolved in 5 ml of MeOH/CH₂Cl₂ (1:1) and 1M HCl (8 mL) in Et₂O solution was added. The solvents were removed *in vacuo* to afford the title salt as a yellow solid.

Example 33



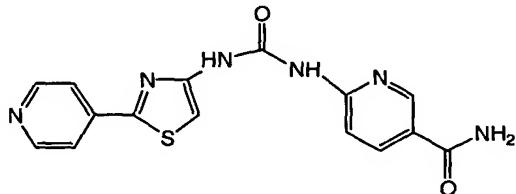
20

N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-[6-[3-(1-morpholinyl)propyl]amino]pyridinyl]urea

A mixture of 2-(4-pyridinyl)-4-thiazolyl-carbonylazide (200 mg, 0.86 mmol) and 2-amino-6-(3-(*N*-morpholinyl)propylamino)pyridine (300 mg, 1.27 mmol) in toluene (8 mL) was heated at 70°C for 1 h, and then at 80°C for 5 h. After the mixture was cooled to RT the solvent was removed *in vacuo* and the product was purified by

chromatography on silica gel (1:10 MeOH(NH₃) /CH₂Cl₂) to afford the title compound as a light yellow solid: m.p. 215-217°C. MS m/z: 440 (M+1). Calc'd. for C₂₁H₂₅N₇O₂S - 439.541.

5

Example 34

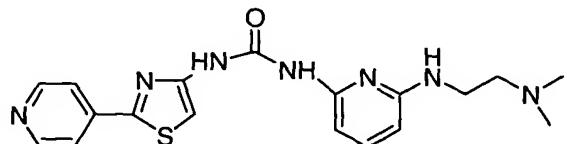
10

[(2-(4-Pyridinyl)-4-thiazolylamino)carbonyl]amino]-2-pyridinyl-5-carboxamide

15

A mixture of 2-(4-pyridinyl)-4-thiazolyl-carbonylazide (100 mg, 0.43 mmol) and 6-aminonicotinamide (200 mg, 1.45 mmol) in toluene (5 mL) was heated at 80°C for 6 h. After the mixture was cooled to RT the solvent was removed *in vacuo* and the crude product was purified by chromatography on silica gel (1:10 MeOH(NH₃) /CH₂Cl₂) to afford the title compound as a light yellow solid: m.p. 255-257°C. MS m/z: 341 (M+1). Calc'd for C₁₅H₁₂N₆O₂S - 340.37.

20

Example 35

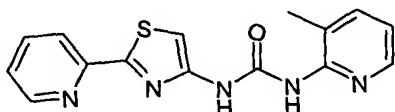
25

N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-[6-(N',N''-aminoethylamino)pyridinyl]urea

A mixture of 2-(4-pyridinyl)-4-thiazolyl-carbonylazide (200 mg, 0.86 mmol) and 2-amino-6-(N,N-dimethylethylenediamino)pyridine (234 mg, 1.30 mmol) in toluene (10 mL) was heated at 70°C for 1 h, and then at 80°C for 5 h. After the mixture was cooled to RT the solvent was removed in vacuo and the crude product was purified by chromatography on silica gel (1:10 MeOH(NH₃)/CH₂Cl₂) to afford the title compound as a light yellow solid: m.p. 210-212°C. MS m/z: 384 (M+1). Calc'd. for C₁₈H₂₁N₇OS - 383.48.

10

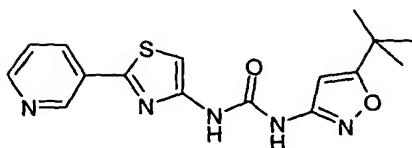
Example 36



15 N-[2-(2-Pyridinyl)-4-thiazolyl]-N'-(3-methylpyridinyl)urea

2-(2-Pyridinyl)-4-thiazolylcarbonylazide (500mg, 2.2 mmol) and 2-amino-3-methylpyridine (183mg, 6.6mmol) were heated in toluene (20 mL) at 100°C for 12 h. After cooling to RT, the solids were collected by filtration and washed first with toluene (2x20 mL) followed by Et₂O (3x10 mL). Recrystallization of the product from MeOH afforded the desired material: m.p. 235-237°C. MS m/z: 312 (M+H). Calc'd. for C₁₅H₁₃N₅OS - 311.368.

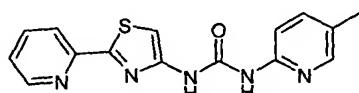
25

Example 37

5

N-[2-(3-Pyridinyl)-4-thiazolyl]-N'-(5-(1,1-dimethylethyl)-3-isoxazolyl)urea

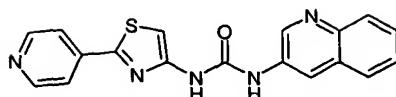
2-(3-Pyridinyl)-4-thiazolylcarbonylazide (300 mg, 1.30 mmol) and 3-amino-5-(*tert*-butyl)isoxazole (491 mg, 3.50 mmol) were heated in toluene (10 mL) at 95°C for 24 h. After cooling to RT, the solids were collected by filtration and washed first with toluene (2x20 mL) followed by cold EtOAc (3x10 mL) to give the product as an off-white solid: m.p. 230-232° C. MS *m/z*: 344 (M+H). Calc'd. for C₁₆H₁₇N₅O₂S - 343.410.

Example 38

20

N-[2-(2-Pyridinyl)-4-thiazolyl]-N'-(5-methylpyridinyl)urea

2-(2-Pyridinyl)-4-thiazolylcarbonylazide (200 mg, 0.87 mmol) and 2-amino-5-methylpyridine (183 mg, 1.7 mmol) were heated in toluene (15 mL) at 100°C for 12 h. After cooling to RT, the solids were collected by filtration and washed first with toluene (2x20mL) followed by Et₂O:EtOAc (3:1) (3x10 mL) to afford the product as a tan solid: m.p. 228-230°C. MS *m/z*: 312 (M+H). Calc'd. for C₁₅H₁₃N₅OS-311.368.

Example 39

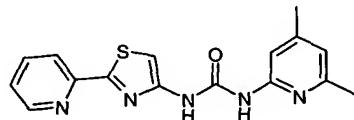
5

N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-3-quinolinylurea

In a manner similar to that described in Example 2, 2-(4-pyridinyl)-4-thiazolylcarbonylazide (53 mg, 0.229 mmol) and 3-aminoquinoline (36 mg, 260 mmol) were heated in toluene (10 mL) to give the product as a pale yellow solid. MS *m/z*: 348.5 (M+H). Calc. for C₁₈H₁₃N₅OS - 347.401.

Example 40

15

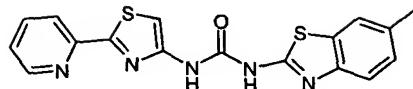
**N-[2-(2-Pyridinyl)-4-thiazolyl]-N'-2-(4,6-dimethylpyridinyl)urea**

20

2-(2-Pyridinyl)-4-thiazolylcarbonylazide (200mg, 0.87mmol) and 2-amino-4,6-dimethylpyridine (210mg, 1.7mmol) were heated in toluene (15 mL) at 100°C for 12 h. After cooling to RT, the solids were collected by filtration and washed first with toluene (2 x 20 mL) followed by Et₂O:EtOAc (3:1) (3 x 10 mL) to afford the product as a tan solid: m.p. 232-234°C. MS *m/z*: 326 (M+H). Calc'd. for C₁₆H₁₅N₅OS - 325.394.

30

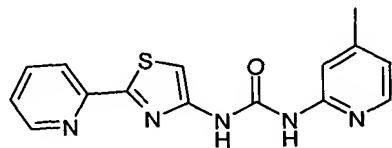
Example 41



5 N-[2-(2-Pyridinyl)-4-thiazolyl]-N'-2-(6-methylbenzthiazolyl)urea

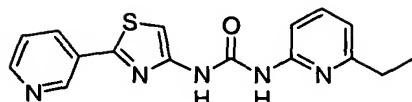
2-(2-Pyridinyl)-4-thiazolylcarbonylazide (200 mg, 0.87 mmol) and 2-amino-6-methylbenzothiazole (279 mg, 1.7 mmol) were heated in toluene (15 mL) at 100°C for 12 h. After cooling to RT, the solids were collected by filtration and washed first with toluene (2 x 20 mL) followed by Et₂O:EtOAc (3:1) (3 x 10 mL) to afford the product as a tan solid: m.p. 263-265°C. MS *m/z*: 312 (M+H). Calc'd. for C₁₇H₁₃N₅OS₂ - 367.456.

Example 42



N-[2-(2-Pyridinyl)-4-thiazolyl]-N'-2-(4-methylpyridinyl)urea

25 2-(2-Pyridinyl)-4-thiazolylcarbonylazide (200 mg, 0.87 mmol) and 2-amino-4-methylpyridine (183 mg, 1.7 mmol) were
 30 heated in toluene (15 mL) at 100°C for 12 h. After cooling to RT, the solids were collected by filtration and washed first with toluene (2 x 20 mL) followed by Et₂O:EtOAc (3:1) (3 x 10 mL) to afford the product as an off-white solid: m.p. 217-219°C. MS *m/z*: 312 (M+H). Calc'd. for C₁₅H₁₃N₅OS - 311.368.

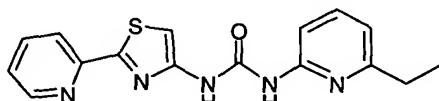
Example 43

5

N-[2-(3-Pyridinyl)-4-thiazolyl]-N'-2-(6-ethylpyridinyl)urea

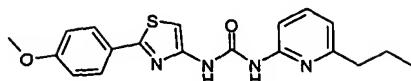
In a manner similar to that described in Example 2, 2-(3-pyridinyl)-4-thiazolylcarbonylazide (186 mg, 0.804 mmol) and 2-amino-6-ethylpyridine (364 mg, 2.78 mmol) were heated in toluene (12 mL) to give the product as a pale yellow solid. MS m/z : 326.5 (M+H). Calc'd. for $C_{16}H_{15}N_5OS$ - 325.395.

15

Example 44

20

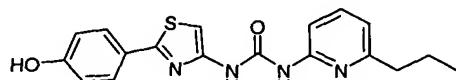
2-(2-Pyridinyl)-4-thiazolylcarbonylazide (200 mg, 0.87 mmol) and 2-amino-6-ethylpyridine (318 mg, 2.6 mmol) were heated in toluene (10 mL) at 100°C for 14 h. After cooling to RT, the solids were collected by filtration and washed first with toluene (2 x 20 mL) followed by Et₂O (2 x 10mL) and cold EtOAc (3 x 5 mL) to give the product as a beige solid: m.p. 213-215°C. MS m/z : 326 (M+H). Calc'd. for $C_{16}H_{15}N_5OS$ - 325.395.

Example 45

5

N-[2-(4-Methoxyphenyl)-4-thiazolyl]-N'-2-(6-propylpyridinyl)urea

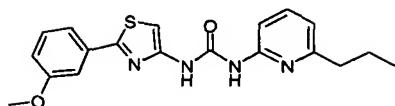
2-(4-Methoxyphenyl)-4-thiazolylcarbonylazide (280 mg, 10 1.1 mmol) and 2-amino-6-n-propylpyridine (439 mg, 3.2 mmol) were heated in toluene (20 mL) at 100°C for 14 h. After cooling to RT, the solids were collected by filtration and washed first with toluene (2x20 mL) followed by Et₂O (2x10 L) and cold EtOAc (3x5 mL) to afford the product as an off-white solid. m.p. 223-225°C. MS m/z: 369 (M+H). Calc'd for C₁₉H₂₀N₄O₂S - 368.461.

Example 46

20

N-[2-(4-Hydroxyphenyl)-4-thiazolyl]-N'-2-(6-propylpyridinyl)urea

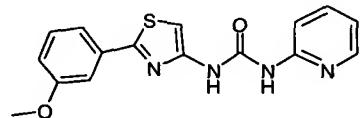
25 To a stirred solution of Example 45 (100 mg, 0.271 mmol) in CH₂Cl₂ (5 mL), boron tribromide was added dropwise at RT. The mixture was stirred for 8 h before adding H₂O (10 ml) and the resulting solids were collected by filtration. This material was washed several times with H₂O 30 and then EtOAc followed by drying *in vacuo* to afford the desired product as a light yellow solid: m.p. 227-229°C. MS m/z: 355 (M+H). Calc'd for C₁₈H₁₈N₄O₂S - 354.434.

Example 47

5

N-[2-(3-Methoxyphenyl)-4-thiazolyl]-N'-2-(6-propylpyridinyl)urea

2-(3-Methoxyphenyl)-4-thiazolylcarbonylazide (1.0 g, 10 3.8 mmol) and 2-amino-6-n-propylpyridine (1.05 g, 7.7 mmol) were heated in toluene (40 mL) at 100°C for 12 h. After cooling to RT, the solids were collected by filtration and washed first with toluene (2x40 mL) followed by cold EtOAc (3x20 mL) to afford the product as a white solid: m.p. 192-194°C. MS *m/z*: 369 (M+H). Calc'd for C₁₉H₂₀N₄O₂S - 368.461.

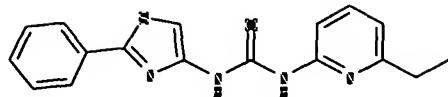
Example 48

20

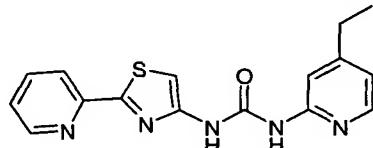
N-[2-(3-Methoxyphenyl)-4-thiazolyl]-N'-2-pyridinylurea

2-(3-Methoxyphenyl)-4-thiazolylcarbonylazide (1.0 g, 3.8 mmol) and 2-aminopyridine (0.72 g, 7.7 mmol) were heated (25 in toluene (40 mL) at 100°C for 12 h. After cooling to RT, the solids were collected by filtration and washed first with toluene (2x40 mL) followed by cold EtOAc (3x20 mL) to afford the product as a white solid: m.p. 201-203°C. MS *m/z*: 327 (M+H). Calc'd for C₁₆H₁₄N₄O₂S - 326.380.

30

Example 495 **N-[2-phenyl-4-thiazolyl]-N'-2-(6-ethylpyridinyl)urea**

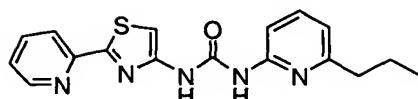
In a manner similar to that described in Example 2, 2-phenyl-4-thiazolylcarbonylazide (150 mg, 0.652 mmol) and 2-amino-6-ethylpyridine (250 mg, 2.05 mmol) were heated in toluene (10 mL) to give the product as a pale yellow solid. MS *m/z*: 325.4 (M+H). Calc'd for C₁₇H₁₆N₄OS - 324.407.

Example 50

15

N-[2-(2-Pyridinyl)-4-thiazolyl]-N'-2-(4-ethylpyridinyl)urea

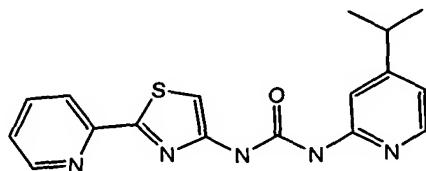
2-(2-Pyridinyl)-4-thiazolylcarbonylazide (200 mg, 0.87 mmol) and 2-amino-4-ethylpyridine (208 mg, 1.7 mmol) were heated in toluene (15 mL) at 100°C for 12 h. After cooling to RT, the solids were collected by filtration and washed first with toluene (2x20 mL) followed by Et₂O:EtOAc (3:1) (3x10 mL) to afford the product as a tan solid: m.p. 196-198°C. MS *m/z*: 326 (M+H). Calc'd. for C₁₆H₁₅N₅OS - 325.395.

Example 51

5

N-[2-(2-Pyridinyl)-4-thiazolyl]-N'-2-(6-propylpyridinyl)urea

2-(2-Pyridinyl)-4-thiazolylcarbonylazide (200 mg, 0.87 mmol) and 2-amino-6-(n-propyl)pyridine (350 mg, 2.6 mmol) were heated in toluene (10mL) at 100°C for 14 h. After cooling to RT, the solids were collected by filtration and washed first with toluene (2x20 mL) followed by Et₂O (2x10 mL) and cold EtOAc (3x5 mL) to give the product as a grayish solid: m.p. 210-212°C. MS m/z: 340 (M+H). Calc'd. for C₁₇H₁₇N₅OS - 339.422.

Example 52

20

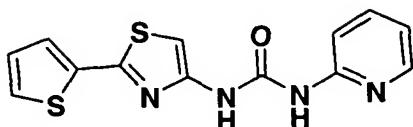
N-[2-(2-Pyridinyl)-4-thiazolyl]-N'-2-[4-(1-methylethyl)pyridinyl]urea

2-(2-Pyridinyl)-4-thiazolylcarbonylazide (300 mg, 1.3 mmol) and 2-amino-4-isopropylpyridine (500 mg, 3.6 mmol) were heated in 10 mL toluene at 100°C for 12 h. After cooling to RT, the solvent was removed by rotary evaporation and the crude oil was purified by column chromatography with hexane:EtOAc (7:3) as eluant to give

the urea as a light yellow solid. MS m/z : 340 (M+H).
Calc'd for $C_{17}H_{17}N_5OS$ - 339.42.

Example 53

5

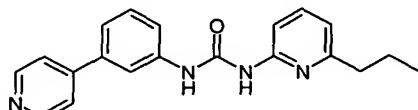


N-[2-(2-Thienyl)-4-thiazolyl]-N'-2-(pyridinyl)urea

10 2-(2-Thienyl)-4-thiazolylcarbonylazide (200 mg, 0.85 mmol) and 2-aminopyridine (154 mg, 1.62 mmol) were heated in 20 mL toluene at 100°C for 16 h. After cooling to RT, the solids were collected by filtration and washed first with toluene (2 x 20 mL) followed by $Et_2O:EtOAc$ (3:1) (3 x 10 mL) to afford the urea as an off-white solid. MS m/z : 303 (M+H). Calc'd for $C_{13}H_{10}N_4OS_2$ - 302.38.

Example 54

20



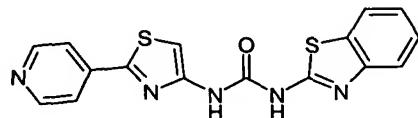
N-[3-(4-Pyridinyl)phenyl]-N'-2-(6-propylpyridinyl)urea

25 To a suspended anhydrous solution of 4-pyridylaniline (180 mg, 1.06 mmol) in dry toluene (8 mL) was added phosgene (0.73 mL, 1.38 mmol, 20% in toluene) followed by DIEA (0.37 mL, 2.11 mmol) under an atmosphere of argon. After stirring for 0.5 h at RT, 2-amino-6-(n-propyl)pyridine (144 mg, 1.06 mmol) in dry toluene (3 mL) was added dropwise into the 30 reaction mixture. The resulting mixture was stirred at RT for 18 h. The organic solvent was removed under vacuum.

The residue was purified by flash chromatography on silica gel using 5% MeOH/CH₂Cl₂ as eluant to obtain the final urea as white solid: m.p. 195-198°C. MS *m/z*: 333.4 (M+H). Calc'd. for C₂₀H₂₀N₄O - 332.405.

5

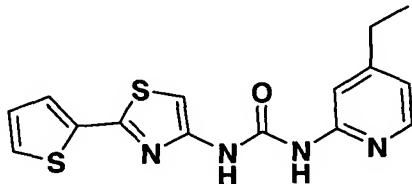
Example 55



10 **N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-benzthiazolylurea**

In a manner similar to that described in Example 2, 2-(4-pyridinyl)-4-thiazolylcarbonylazide (52 mg, 0.225 mmol) and 2-aminobenzothiazole (41 mg, 0.273 mmol) were heated in toluene (10 mL) to give the product as a pale yellow solid. MS *m/z*: 354.4 (M+H). Calc'd. for C₁₆H₁₁N₅OS₂ - 353.427.

15 Example 56



20

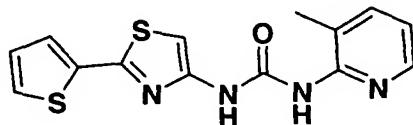
N-[2-(2-Thienyl)-4-thiazolyl]-N'-2-(4-ethylpyridinyl)urea

25 2-(2-Thienyl)-4-thiazolylcarbonylazide (500 mg, 2.1 mmol) and 2-amino-4-ethylpyridine (512 mg, 4.2 mmol) were heated in 15 mL toluene at 100°C for 16 h. After cooling to RT, the solids were collected by filtration and washed first with toluene (2x20 mL) followed by Et₂O:EtOAc (3:1) (3

x 10 mL) to afford the urea as an off-white solid. MS *m/z*: 331 (M+H). Calc'd for C₁₅H₁₄N₄OS₂ - 330.435.

Example 57

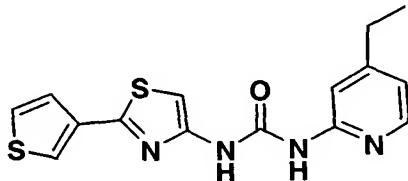
5



N-[2-(2-Thienyl)-4-thiazolyl]-N'-2-(3-methylpyridinyl)urea

10 2-(2-Thienyl)-4-thiazolylcarbonylazide (500 mg, 2.1 mmol) and 2-amino-3-methylpyridine (449 mg, 4.2 mmol) were heated in 15 mL toluene at 100°C for 16 h. After cooling to RT, the solids were collected by filtration and washed first with toluene (2x20 mL) followed by Et₂O:EtOAc (3:1) (3x10 mL) to afford the urea as an off-white solid. MS *m/z*: 317 (M+H). Calc'd for C₁₄H₁₂N₄OS₂ - 316.408.

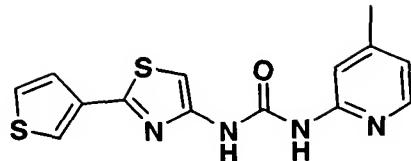
Example 58



20

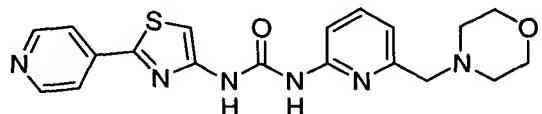
N-[2-(3-Thienyl)-4-thiazolyl]-N'-2-(4-ethylpyridinyl)urea

20 2-(3-Thienyl)-4-thiazolylcarbonylazide (200 mg, 0.85 mmol) and 2-amino-4-ethylpyridine (310 mg, 2.54 mmol) were heated in 10 mL toluene at 100°C for 16 h. After cooling to RT, the solids were collected by filtration and washed first with toluene (2x20 mL) followed by Et₂O:EtOAc (3:1; (3x10 mL) to afford the product as an off-white solid. MS *m/z*: 331 (M+H). Calc'd for C₁₅H₁₄N₄OS₂ - 330.435.

Example 595 **N-[2-(3-Thienyl)-4-thiazolyl]-N'-2-(4-methylpyridinyl)urea**

2-(3-Thienyl)-4-thiazolylcarbonylazide (200 mg, 0.85 mmol) and 2-amino-4-methylpyridine (272 mg, 2.54 mmol) were heated in 10 mL toluene at 100°C for 16 h. After cooling to 10 RT, the solids were collected by filtration and washed first with toluene (2x20mL) followed by Et₂O:EtOAc (3:1) (3x10mL) to afford the product as an off-white solid. MS *m/z*: 317 (M+H). Calc'd for C₁₄H₁₂N₄OS₂ - 316.408.

15

Example 60

N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-[6-(1-morpholinylmethyl)pyridinyl]urea

20

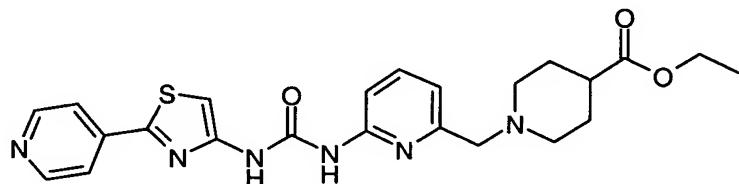
2-(4-Pyridinyl)-4-thiazolylcarbonylazide (100 mg, 0.43 mmol) in dry toluene (10 mL) was heated to 85°C under N₂ and maintained at for 5 min. A solution of 6-morpholin-4-ylmethyl-pyridin-2-ylamine (101 mg, 0.52 mmol) in dry toluene (2 mL) was added dropwise via syringe and the resulting mixture was heated at 100°C for 12 h. After cooling to RT, a precipitate formed and was collected,

rinsing with hexane to give a white solid. MS m/z : 397.3 (M+H). Calc'd for $C_{19}H_{20}N_6O_2S$: 396.14.

5 The following compounds were prepared from the corresponding amines in a manner similar to that described above for Example 60.

Example 61

10



Ethyl 1-{6-[3-(2-(pyridin-4-yl)thiazol-4-yl)ureido]-pyridin-2-ylmethyl}-piperidine-4-carboxylate

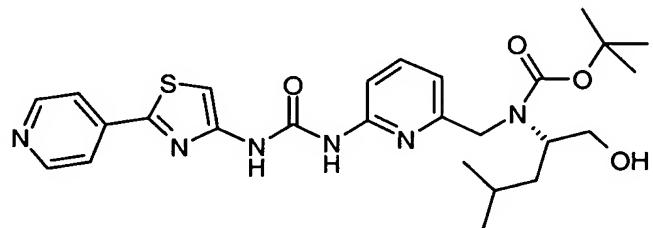
15

2-(4-Pridinyl)-4-thiazolcarbonylazide (182 mg, 0.87 mmol) heated with ethyl 1-(6-aminopyridin-2-ylmethyl)-piperidine-4-carboxylate (230 mg, 0.87 mmol) in dry toluene (15 mL) gave the final urea. MS m/z : 466.9 (M+H). Calc'd. for $C_{23}H_{26}N_6O_3S$ - 466.50.

20

Example 62

25

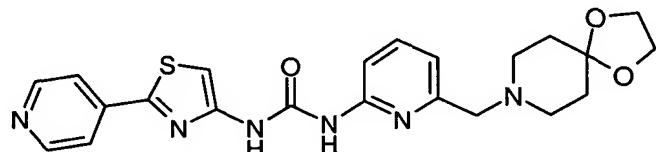


tert-Butyl (1-hydroxymethyl-3-methyl-butyl)-{6-[3-(2-pyridin-4-yl-thiazol-4-yl)-ureido]-pyridin-2-ylmethyl}-carbamate

2-(4-Pyridinyl)-4-thiazolcarbonylazide (343 mg, 1.48 mmol) was heated with 2-amino-6-[N'-*tert*-butoxycarbonyl-N'-2-(1-hydroxy-4-methyl)pentylamino]methylpyridine (480 mg, 1.48 mmol) in dry toluene (20 mL) to yield the final 5 compound as pale yellow solid. MS *m/z*: 527.6 (M+H). Calc'd. for C₂₆H₃₄N₆O₄S - 526.66.

Example 63

10



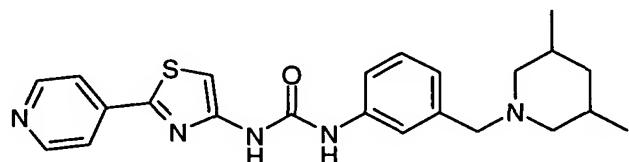
1-[6-(1,4-Dioxa-8-aza-spiro[4.5]dec-8-ylmethyl)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

15

2-(4-Pyridinyl)-4-thiazolcarbonylazide (420 mg, 2.01 mmol) was heated with 2-amino-6-(4-ethoxyacetal)-piperidinylmethyl pyridine (500 mg, 2.01 mmol) in dry toluene (30 mL) to yield the final compound as yellow solid. MS *m/z*: 452.9 (M+H). Calc'd. for C₂₂H₂₄N₆O₃S - 452.23.

20

Example 64

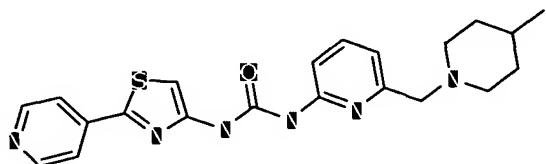


25

1-[6-(3,5-Dimethylpiperidin-1-ylmethyl)pyridin-2-yl]-3-(2-pyridin-4-ylthiazol-4-yl)urea

2-(4-Pyridinyl)-4-thiazolcarbonylazide (200 mg, 0.867 mmol) was heated with 2-amino-6-(3,5-dimethyl)piperidinylmethylpyridine (190 mg, 0.867 mmol) in dry toluene (20 mL) to yield the final compound as yellow solid. MS m/z : 423.2 (M+H). Calc'd. for $C_{22}H_{26}N_6OS$ - 422.0.

Example 65



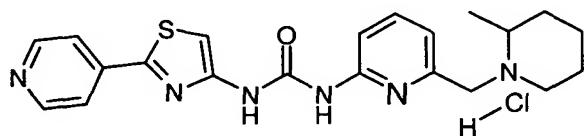
10

1-[6-(4-Methylpiperidin-1-ylmethyl)pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea

2-(4-Pyridinyl)-4-thiazolcarbonylazide (348 mg, 1.51 mmol) was heated with 2-amino-6-(4-methyl)piperidinylmethylpyridine (310 mg, 1.51 mmol) in dry toluene (20 mL) to yield the final compound as pale yellow solid. MS m/z : 409.5 (M+H). Calc'd. for $C_{21}H_{24}N_6OS$ - 408.52.

20

Example 66



25

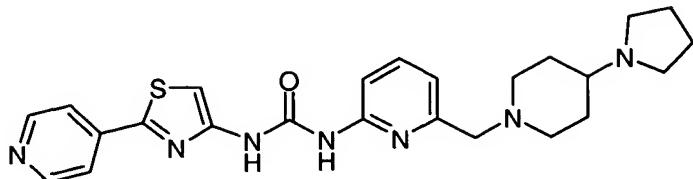
1-[6-(2-Methylpiperidin-1-ylmethyl)pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea

2-(4-Pyridinyl)-4-thiazolcarbonylazide (101 mg, 0.44 mmol) was heated with 2-amino-6-(2-methyl)piperidinylmethylpyridine (90 mg, 0.44 mmol) in dry toluene (15 mL) to yield

the final compound as pale yellow solid . MS m/z : 409.6 (M+H) . Calc'd. for $C_{21}H_{24}N_6OS$ - 408.52.

Example 67

5

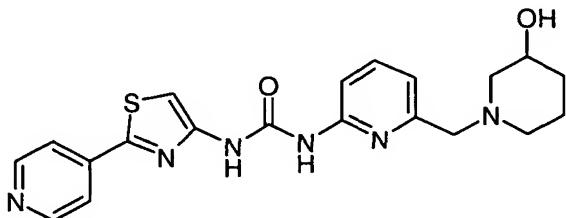


1-(2-Pyridin-4-yl-thiazol-4-yl)-3-[6-(4-pyrrolidin-1-ylmethyl)-pyridin-2-yl]-urea

10 2-(4-pyridinyl)-4-thiazolcarbonylazide (293 mg, 1.43 mmol) was heated with 2-amino-6-[4-(1-pyrrolidinyl)-piperidinylmethyl]pyridine (330 mg, 1.43 mmol) in dry toluene (20 mL) to yield the final compound as pale yellow solid. MS m/z : 464.2 (M+H) . Calc'd. for $C_{24}H_{29}N_7OS$ - 463.

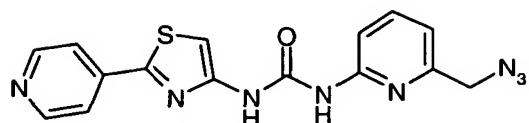
15

Example 68



20 **1-[6-(3-Hydroxy-piperidin-1-ylmethyl)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea**

25 2-(4-Pyridinyl)-4-thiazolcarbonylazide (312 mg, 1.35 mmol) was heated with 2-amino-6-(3-hydroxy)-piperidinylmethyl pyridine (280 mg, 1.35 mmol) in dry toluene (20 mL) to yield the final compound as yellow solid. MS m/z : 410.9 (M+H) . Calc'd. for $C_{20}H_{22}N_6O_2S$ - 410.5.

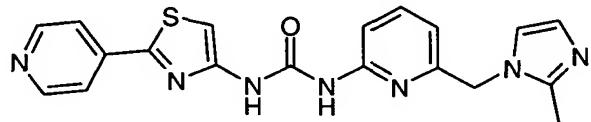
Example 69

5

N-(6-azidomethyl-2-pyridyl)-N'-(2-(4-pyridinyl)-4-thiazolyl)urea

2-(4-Pyridinyl)-4-thiazolcarbonylazide (400 mg, 1.73 mmol) was heated with 2-amino-6-azidomethyl-pyridine (258 mg, 1.73 mmol) in dry toluene (15 mL) to yield the final compound as yellow solid. MS m/z : 353.4 (M+H). Calc'd. for $C_{15}H_{12}N_8OS$ - 352.38.

15

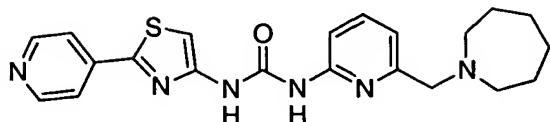
Example 70

20

1-[6-(2-Methyl-imidazol-1-ylmethyl)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

2-(4-Pyridinyl)-4-thiazolcarbonylazide (110 mg, 0.48 mmol) was heated with 2-amino-6-[2-methylimidazol-1-yl]methyl-pyridine (90 mg, 0.48 mmol) in dry toluene (15 mL) to yield the final compound as white solid. MS m/z : 392.4 (M+H). Calc'd. for $C_{19}H_{17}N_7OS$ - 391.45.

30

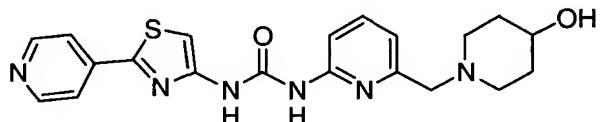
Example 71

5 **1-(6-Azepan-1-ylmethyl-pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)urea**

2-(4-Pyridinyl)-4-thiazolcarbonylazide (150 mg, 0.65 mmol) and 2-amino-6-azaperhydroepinylmethylpyridine (147 mg, 10 0.71 mmol) in dry toluene (15 mL) were heated at 100°C for 12 h to give a pale yellow solid. MS *m/z*: 409.1 (M+H). Calc'd for C₂₁H₂₄N₆OS - 408.52.

Example 72

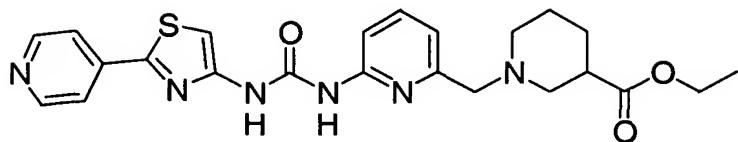
15



1- [6-(4-Hydroxy-piperidin-1-ylmethyl)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

20

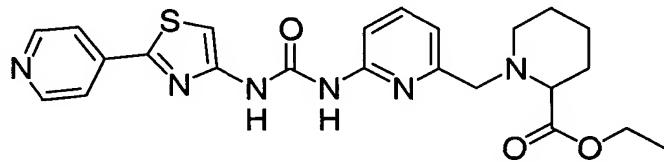
2-(4-Pyridinyl)-4-thiazolcarbonylazide (265 mg, 1.27 mmol) and 2-amino-6-(4-hydroxy)piperidyl-methylpyridine (220 mg, 1.06 mmol) in dry toluene (15 mL) were heated at 100°C for 12 h to give a pale yellow solid which was 25 recrystallized from CHCl₃/MeOH/hexane (94:2:1) to give a white solid. MS *m/z*: 410.9 (M+H). Calc'd for C₂₀H₂₂N₆O₂S - 410.50.

Example 73

5

Ethyl 1-[6-[3-(2-pyridin-4-yl-thiazol-4-yl)ureido]-pyridin-2-ylmethyl]piperidine-3-carboxylate

2-(4-Pyridinyl)-4-thiazolcarbonylazide (150 mg, 0.65 mmol) and 2-amino-ethyl(6-piperidylmethyl-pyridinyl)-3-carboxylate (170 mg, 0.65 mmol) in dry toluene (15 mL) were heated at 100°C for 12 h to give a pale yellow solid which was purified by chromatography on silica gel (CH₂Cl₂/MeOH, 95:5) to give a white solid. MS *m/z*: 467.1 (M+H). Calc'd for C₂₃H₂₆N₆O₃S - 466.56.

Example 74

20

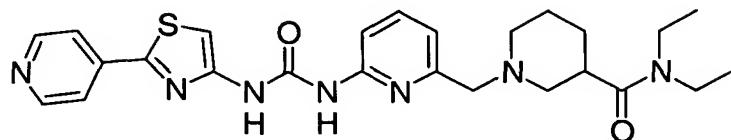
Ethyl 1-[6-[3-(2-(pyridin-4-yl)thiazol-4-yl)ureido]-pyridin-2-ylmethyl]piperidine-2-carboxylate

2-(4-Pyridinyl)-4-thiazolcarbonylazide (483 mg, 2.09 mmol) and ethyl 2-amino-(6-piperidylmethyl-pyridinyl)-2-carboxylate (550 mg, 2.09 mmol) in dry toluene (20 mL) were heated at 100°C for 8 h to give a pale yellow solid which was purified by chromatography on silica gel (CH₂Cl₂/MeOH,

95:5) to give a white solid. MS m/z : 466.9 (M+H). Calc'd for $C_{23}H_{26}N_6O_3S$ - 466.56.

Example 75

5



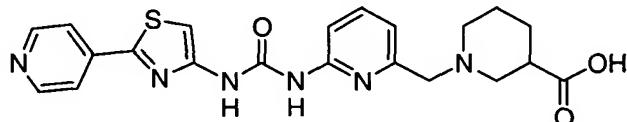
N,N-Diethyl 1-{6-[3-(2-pyridin-4-yl-thiazol-4-yl)-ureido]pyridin-2-ylmethyl}piperidine-3-carboxamide

10

2-(4-Pyridinyl)-4-thiazolcarbonylazide (320 mg, 1.38 mmol) and 2-amino-6-[$(N',N''$ -diethylcarbamoyl)-piperidylmethyl]-3-carboxamide (400 mg, 1.38 mmol) in dry toluene (25 mL) were heated at 100°C for 12 h to give a pale yellow solid which was purified by chromatography on silica gel ($CH_2Cl_2/MeOH$, 95:5) to give the urea as a white solid. MS m/z : 494.1 (M+H). Calc'd for $C_{25}H_{31}N_7O_2S$ - 493.63.

Example 76

20



1-{6-[3-(2-Pyridin-4-yl-thiazol-4-yl)-ureido]-pyridin-2-ylmethyl}-piperidine-3-carboxylic acid

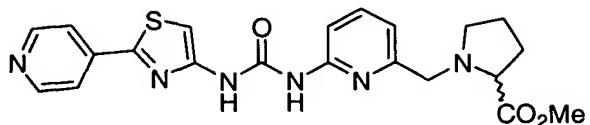
25

2-(4-Pyridinyl)-4-thiazolcarbonylazide (196 mg, 0.85 mmol) and 2-amino-6-(piperidylmethylpyridinyl)-3-carboxylate (200 mg, 0.85 mmol) in dry toluene (10 mL) were heated at 100°C for 8 h to give a pale yellow solid which was purified by chromatography on silica gel ($CH_2Cl_2/MeOH$, 95:5) to give

a white solid. MS m/z : 437.9 (M+H). Calc'd for $C_{21}H_{22}N_6O_3S$ - 438.51.

Example 77

5



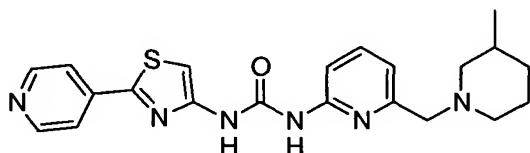
Methyl 1-{6-[3-(2-pyridin-4-yl-thiazol-4-yl)ureido]-pyridin-2-ylmethyl}-pyrrolidine-2-carboxylate

10

2-(4-Pyridinyl)-4-thiazolcarbonylazide (104 mg, 0.45 mmol) and 2-amino-6-(2-methoxycarbonyl)-pyrrolidinylmethylpyridine (105 mg, 0.45 mmol) in dry toluene (10 mL) were heated at 100°C for 12 h to give a pale yellow solid which was purified by chromatography on silica gel (CHCl₃/MeOH, 99:5) to give a white solid. MS m/z : 438.7 (M+H). Calc'd for $C_{21}H_{22}N_6O_3S$ - 438.51.

Example 78

20



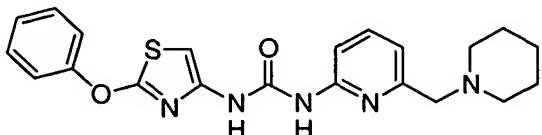
1-[6-(3-Methyl-piperidin-1-ylmethyl)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

25

2-(4-Pyridinyl)-4-thiazolcarbonylazide (259 mg, 1.12 mmol) and 2-amino-6-(3-methyl)piperidinylmethyl-pyridine (230 mg, 1.12 mmol) in dry toluene (15 mL) were heated at 100°C for 12 h to give a pale yellow solid which was

purified by chromatography on silica gel (CHCl₃/MeOH, 99:5) to give a white solid. MS *m/z*: 408.8 (M+H). Calc'd for C₂₁H₂₄N₆OS - 408.53.

5

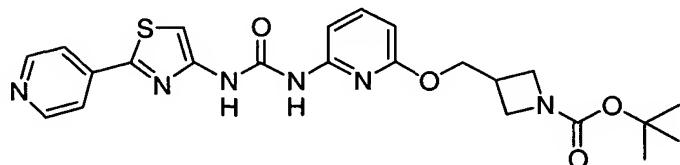
Example 79

10

1-(2-Phenoxy-thiazol-4-yl)-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)-urea

MS *m/z*: 410 (M+H). Calc'd for C₂₁H₂₃N₅O₂S: 409.16.

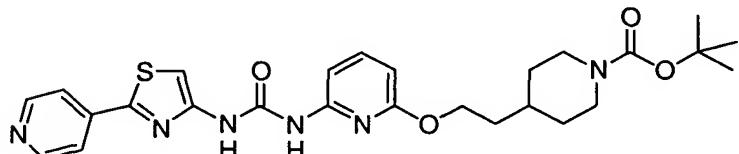
15

Example 80

20

MS *m/z*: 483 (M+H). Calc'd for C₂₃H₂₆N₆O₄S: 482.17.

25

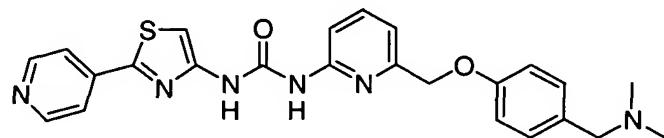
Example 81

**tert Butyl 4-(2-{6-[3-(2-pyridin-4-yl-thiazol-4-yl)-
ur idolpyridin-2-yloxy}ethyl)piperidine-1-carboxylate**

MS *m/z*: 525 (M+H). Calc'd for C₂₆H₃₂N₆O₄S: 524.22

5

Example 82

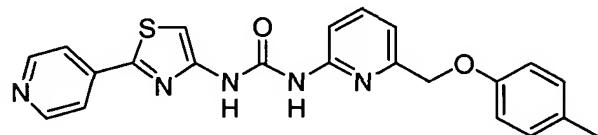


10 **1-[6-(4-Dimethylaminomethyl-phenoxymethyl)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea**

MS *m/z*: 461 (M+H). Calc'd for C₂₄H₂₄N₆O₂S: 460.17.

15

Example 83

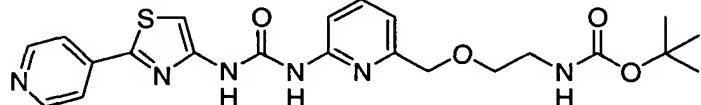


20 **1-(2-Pyridin-4-yl-thiazol-4-yl)-3-(6-(4-methylphenyl)oxymethylpyridin-2-yl)urea**

MS *m/z*: 416 (M-H). Calc'd for C₂₂H₁₉N₅O₂S: 417.13.

25

Example 84

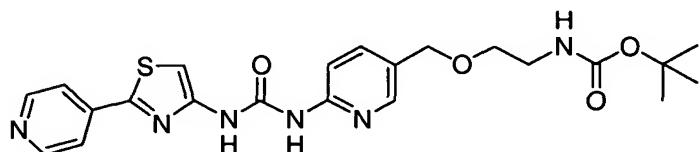


t rt Butyl (2-{6-[3-(2-pyridin-4-yl-thiazol-4-yl)-ureido]pyridin-2-ylmethoxy}ethyl)carbamate

MS *m/z*: 471 (M+H). Calc'd for C₂₂H₂₆N₆O₄S: 470.17.

5

Example 85



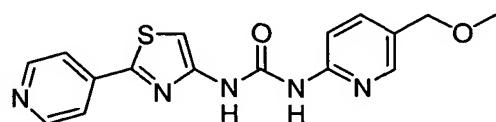
10

tert Butyl (2-{6-[3-(2-pyridin-4-yl-thiazol-4-yl)-ureido]pyridin-3-ylmethoxy}ethyl)carbamate

MS *m/z*: 471 (M+H). Calc'd for C₂₂H₂₆N₆O₄S: 470.17.

15

Example 86



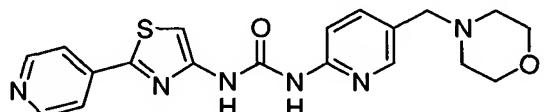
20

1-(5-Methoxymethyl-pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

MS *m/z*: 342 (M+H). Calc'd for C₁₆H₁₅N₅O₂S: 341.09.

Example 87

25

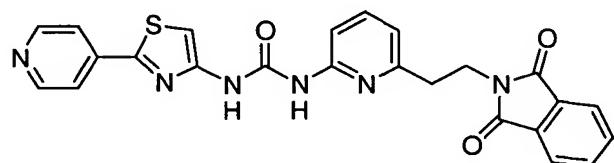


1-(5-Morpholin-4-ylmethyl-pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)urea

MS *m/z*: 397 (M+H). Calc'd for C₁₉H₂₀N₆O₂S: 396.14.

5

Example 88



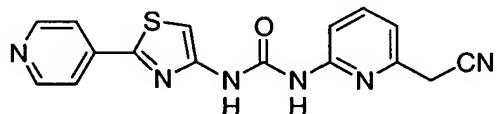
10 **1-{6-[2-phthalimidylethyl]pyridin-2-yl}-3-(2-pyridin-4-yl-thiazol-4-yl)urea**

Prepared in a manner similar to that described in Example 60 from 3-(4-pyridyl)-thiazole acyl-azide (103 mg, 0.56 mmol) and 2-amino-6-ethylphthalimidylpyridine (150 mg, 0.56 mmol) in toluene (10 mL). Concentrated *in vacuo* to afford a yellow solid which was treated with EtOH (10 mL) and filtered to give the title compound as a yellow solid.

MS *m/z*: 470.9 (M+H). Calc'd for C₂₄H₁₈N₆O₃S: 470.12.

20

Example 89



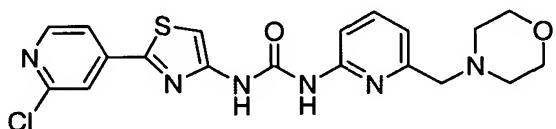
25 **1-(6-Cyanomethylpyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)urea**

Prepared in a manner similar to that described in Example 60 from 2-amino-6-methylnitrile-pyridine (0.32 g,

2.4 mmol) and 3-(4-pyridyl)-4-thiazole acylazide (0.51 g, 2.2 mmol). After 1.5 h, yellow solid precipitated out of toluene solution. The mixture was cooled to RT and the solid filtered. Purified by silica flash chromatography (3% 5 MeOH/CH₂Cl₂) to afford the title compound as a white solid. MS m/z: 337.1 (M+H). Calc'd for C₁₆H₁₂N₆OS: 336.08.

Example 90

10

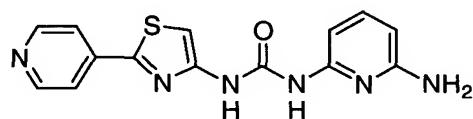


1-[2-(2-Chloropyridin-4-yl)thiazol-4-yl]-3-(6-morpholin-4-ylmethyl)pyridin-2-yl]urea

15 Prepared in a manner similar to that described in Example 60 from 3-(4-pyridyl)-4-thiazole acyl azide (0.51 g, 1.9 mmol) and 2-amino-6-methylmorpholino-pyridine (0.42 g, 2.2 mmol) in toluene (50 mL). After 3 h, the reaction mixture was cooled to RT and filtered to afford the title 20 compound as a light purple solid. MS m/z: 431.0 (M+H). Calc'd for C₁₉H₁₉ClN₆O₂S: 430.10.

Example 91

25

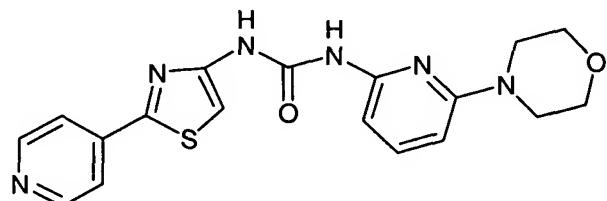


1-(6-Aminopyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)urea

30 Prepared in a manner similar to that described in Example 60 from 3-(4-pyridyl)-4-thiazole-acyl azide (148 mg,

0.64 mmol) and 2,6-diaminopyridine (77 mg, 0.70 mmol, Aldrich) in toluene (10 mL). After 2 h, a yellow precipitate formed. The reaction mixture was cooled and filtered to afford the title compound as a yellow solid. MS 5 m/z: 180 (M+H). Calc'd for $C_{14}H_{12}N_6OS$: 312.08.

Example 92



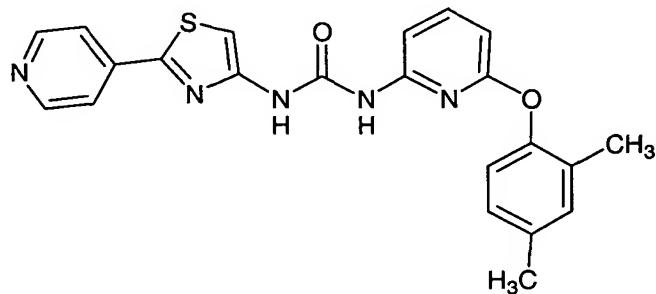
10

1-(6-Morpholin-4-yl-pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)urea

EI-MS m/z 383.4 (M+H). Calc'd for $C_{18}H_{18}N_6O_2S$: 382.12.

15

Example 93



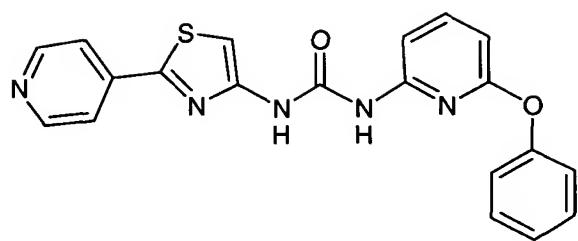
20

1-[6-(2,4-Dimethylphenoxy)pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea

EI-MS m/z 418.5 (M+H). Calc'd for $C_{22}H_{19}N_5O_2S$: 417.13.

25

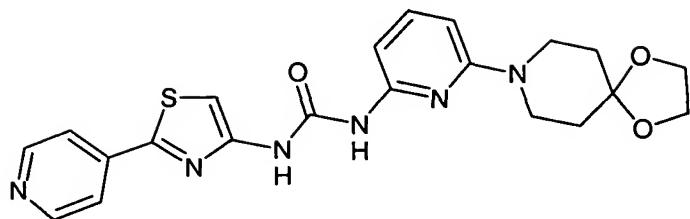
Example 94



1-(6-Phenoxy)pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-

5 **yl)urea**

EI-MS m/z 390.4 ($M+H$). Calc'd for $C_{20}H_{15}N_5O_2S$: 389.09.3

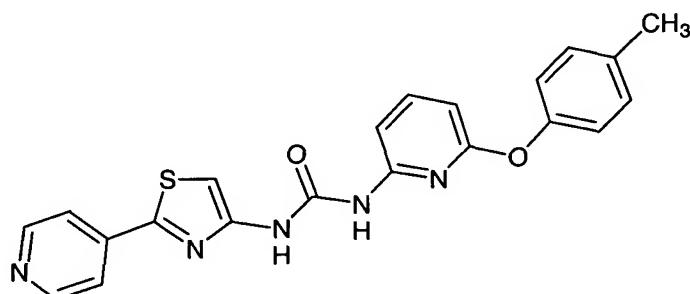
Example 95

5 **1-[6-(1,4-Dioxa-8-aza-spiro[4.5]dec-8-yl)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea**

Prepared in a manner similar to that described in
 Example 60 using 2-(4-pyridinyl)-4-thiazolcarbonylazide and
 10 the requisite 2-aminopyridine. EI-MS m/z 439.5 (M+H).
 Calc'd for $C_{21}H_{22}N_6O_3S$: 438.15.

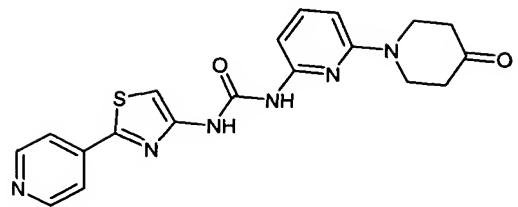
Example 96

15



1-(2-Pyridin-4-yl-thiazol-4-yl)-3-(6-p-tolyloxy-pyridin-2-yl)-urea

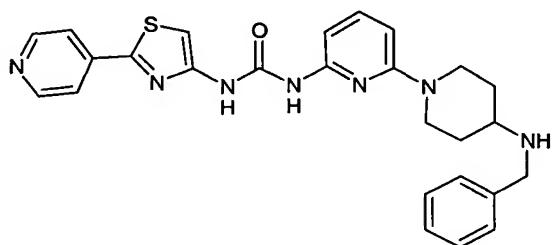
20 EI-MS m/z 404.4 (M+H). Calc'd for $C_{21}H_{17}N_5O_2S$: 403.11.

Example 97

5 **1-(4-Oxo-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-6'-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)-urea**

EI-MS m/z 395.4 (M+H). Calc'd for C₁₉H₁₈N₆O₂S: 394.12.

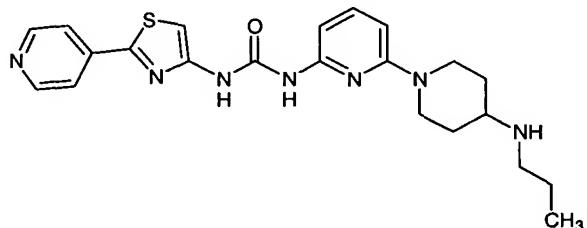
10

Example 98

15 **1-(4-Benzylamino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-6'-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)-urea**

EI-MS m/z 486.7 (M+H). Calc'd for C₂₆H₂₇N₇OS: 485.20.

20

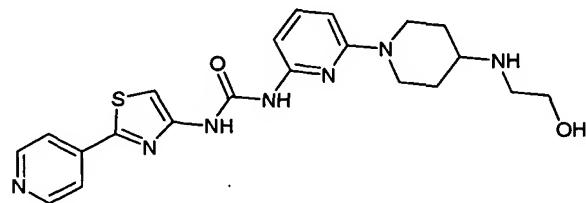
Example 99

1-(4-Propylamino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-6'-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

EI-MS m/z 438.6 (M+H). Calc'd for C₂₂H₂₇N₇OS: 437.20.

5

Example 100

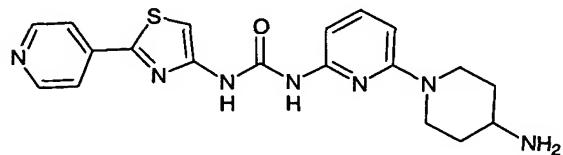


10 **1-[4-(2-Hydroxy-ethylamino)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-6'-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea**

EI-MS m/z 440.5 (M+H). Calc'd for C₂₁H₂₅N₇O₂S: 439.18.

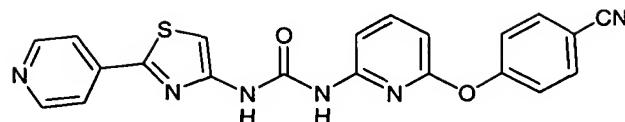
15

Example 101



20 **1-(4-Amino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-6'-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)-urea**

EI-MS m/z 396.6 (M+H). Calc'd for C₁₉H₂₁N₇OS: 395.15.

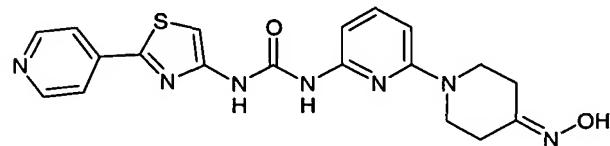
Example 102

5

1-[6-(4-Cyanophenoxy)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea

EI-MS m/z 415.5 (M+H). Calc'd for C₂₁H₁₄N₆O₂S: 414.09.

10

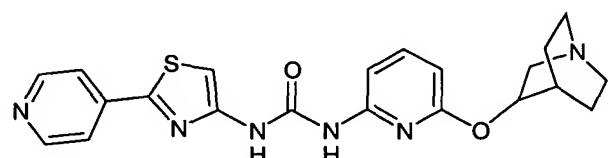
Example 103

15

1-(4-Hydroxyimino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-6'-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)urea

EI-MS m/z 410.4 (M+H). Calc'd for C₁₉H₁₉N₇O₂S: 409.13.

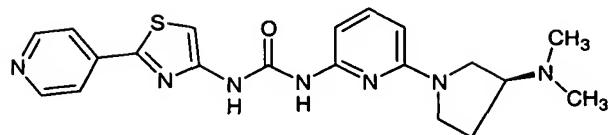
20

Example 104

25

1-[6-(1-Aza-bicyclo[2.2.2]oct-3-yloxy)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea

EI-MS m/z 423.6 (M+H). Calc'd for C₂₁H₂₂N₆O₂S: 422.15.

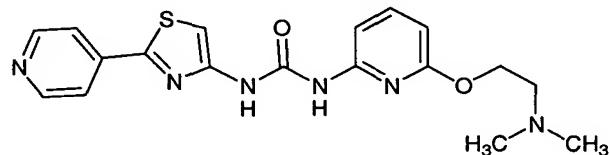
Example 105

5

1-[6-(3-Dimethylamino-pyrrolidin-1-yl)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

EI-MS m/z 410.5 (M+H). Calc'd for C₂₀H₂₃N₇OS: 409.17.

10

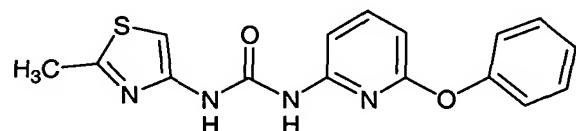
Example 106

15

1-[6-(2-Dimethylamino-ethoxy)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

EI-MS m/z 385.5 (M+H). Calc'd for C₁₈H₂₀N₆O₂S: 384.14.

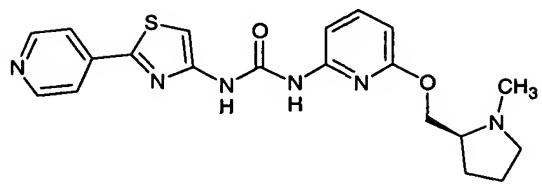
20

Example 107

25

1-(2-Methylthiazol-4-yl)-3-(6-phenoxy-pyridin-2-yl)urea

EI-MS m/z 327.4 (M+H). Calc'd for C₁₆H₁₄N₄O₂S: 326.08.

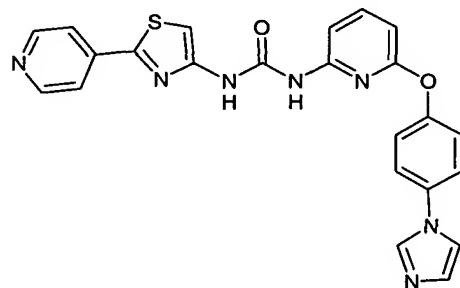
Example 108

5

1-[6-(1-Methylpyrrolidin-2-ylmethoxy)pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea

EI-MS m/z 411.4 (M+H). Calc'd for $C_{20}H_{22}N_6O_2S$: 410.15.

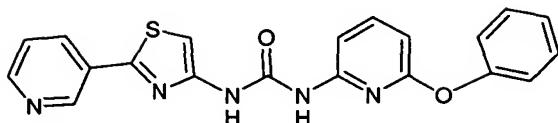
10

Example 109

15 **1-[6-(4-Imidazol-1-yl-phenoxy)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea**

EI-MS m/z 456.6 (M+H). Calc'd for $C_{23}H_{17}N_7O_2S$: 455.12.

20

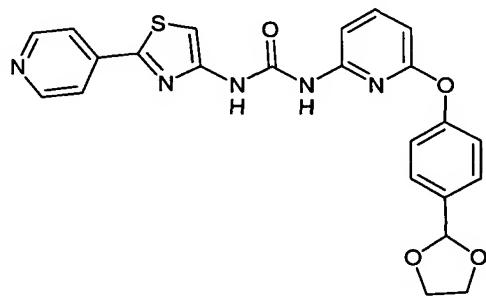
Example 110

5

1-(6-Phenoxy)pyridin-2-yl)-3-(2-pyridin-3-yl-thiazol-4-yl)urea

EI-MS m/z 390.5 (M+H). Calc'd for C₂₀H₁₅N₅O₂S: 389.09.

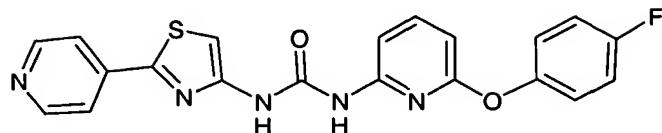
10

Example 111

15

1-[6-(4-[1,3]Dioxolan-2-yl-phenoxy)pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea

EI-MS m/z 462.5 (M+H). Calc'd for C₂₃H₁₉N₅O₄S: 461.12.

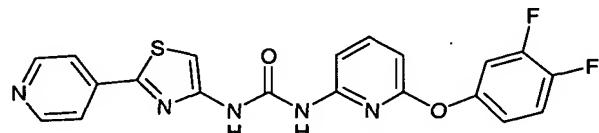
Example 112

5

1-[6-(4-Fluorophenoxy)pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea

EI-MS m/z 408.5 (M+H). Calc'd for $C_{20}H_{14}FN_5O_2S$: 407.09.

10

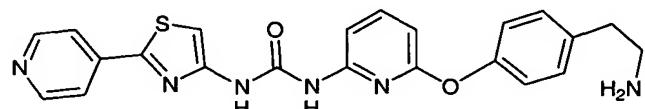
Example 113

15

1-[6-(3,4-Difluorophenoxy)pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea

EI-MS m/z 426.5 (M+H). Calc'd for $C_{20}H_{13}F_2N_5O_2S$: 425.08.

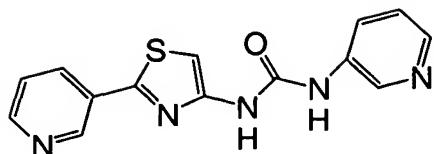
20

Example 114

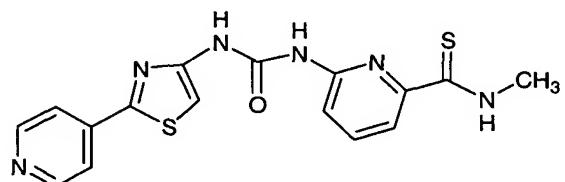
25

1-[6-[4-(2-Aminoethyl)phenoxy]pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea

EI-MS m/z 433.5 (M+H). Calc'd for $C_{22}H_{20}N_6O_2S$: 432.14.

Example 1155 **1-Pyridin-3-yl-3-(2-pyridin-3-yl-thiazol-4-yl)-urea**EI-MS m/z 396.6 (M+H). Calc'd for C₁₄H₁₁N₅OS: 297.07.Example 116

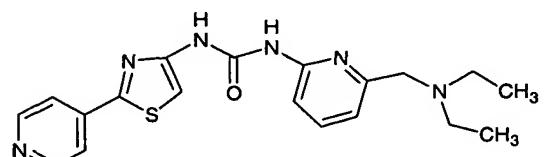
10

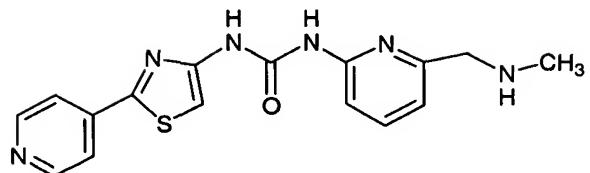
15 **6-[3-(2-Pyridin-4-yl-thiazol-4-yl)-ureido]-pyridine-2-carbothioic acid methylamide**

15

EI-MS m/z 371.5 (M+H). Calc'd for C₁₆H₁₄N₆OS₂: 370.07.Example 117

20

25 **1-(6-Diethylaminomethyl-pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)urea**EI-MS m/z 383.5 (M+H). Calc'd for C₁₉H₂₂N₆OS: 382.16.

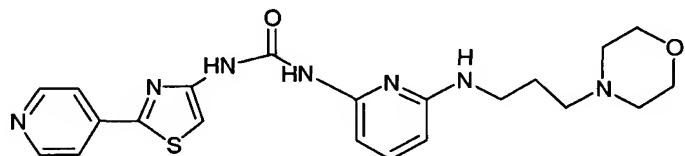
Example 118

5

1-(6-Methylaminomethyl-pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)urea

EI-MS m/z 341.4 (M+H). Calc'd for C₁₆H₁₆N₆OS: 340.11.

10

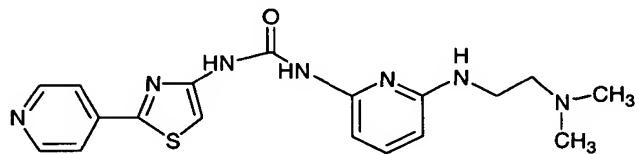
Example 119

15

1-[6-(3-Morpholin-4-yl-propylamino)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

EI-MS m/z 440.4 (M+H). Calc'd for C₂₁H₂₅N₇O₂S: 439.18.

20

Example 120

25

1-[6-(2-Dimethylamino-ethylamino)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

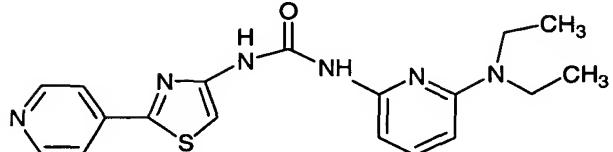
A-706B

- 224 -

EI-MS m/z 384.5 (M+H). Calc'd for C₁₈H₂₁N₇OS: 383.15.

Example 121

5

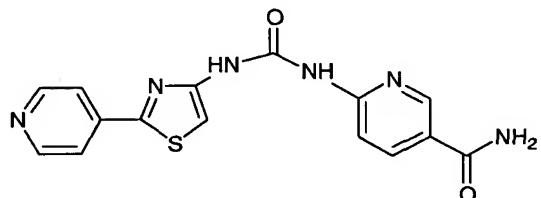


1-(6-Diethylamino-pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

10 EI-MS m/z 369.3 (M+H). Calc'd for C₁₈H₂₀N₆OS: 368.14.

Example 122

15



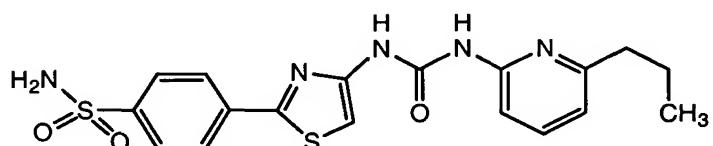
6-[3-(2-Pyridin-4-yl-thiazol-4-yl)-ureido]nicotinamide

EI-MS m/z 341.3 (M+H). Calc'd for C₁₅H₁₂N₆O₂S: 340.07.

20

Example 123

25

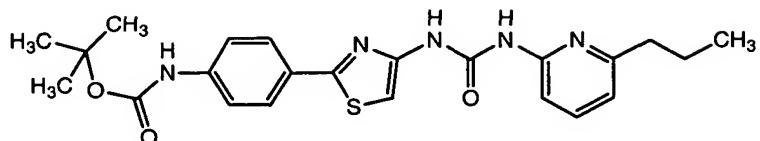


4-{4-[3-(6-Propylpyridin-2-yl)ureido]thiazol-2-yl}-benzen sulfonamide

EI-MS m/z 418.5 (M+H). Calc'd for C₁₈H₁₉N₅O₃S₂: 417.09.

Example 124

5



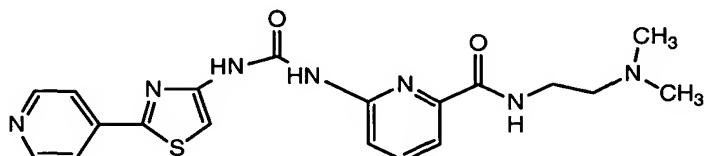
tert Butyl (4-{4-[3-(6-Propylpyridin-2-yl)ureido]-thiazol-2-yl}phenyl)carbamate

10

EI-MS m/z 454.6 (M+H). Calc'd for C₂₃H₂₇N₅O₃S: 453.18.

Example 125

15

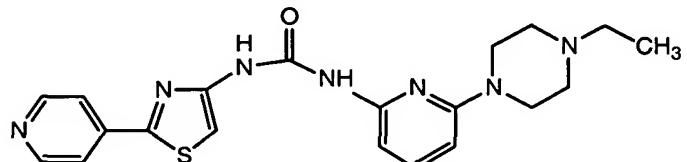


2-Dimethylaminoethyl 6-[3-(2-pyridin-4-yl-thiazol-4-yl)ureido]pyridine-2-carboxamide

20 EI-MS m/z 412.5 (M+H). Calcd for C₁₉H₂₁N₇O₂S: 411.15.

Example 126

25

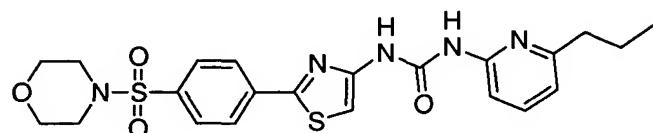


1-[6-(4-Ethylpyridin-1-yl)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea

EI-MS m/z 410.6 (M+H). Calc'd for C₂₀H₂₃N₇OS: 409.17.

5

Example 127

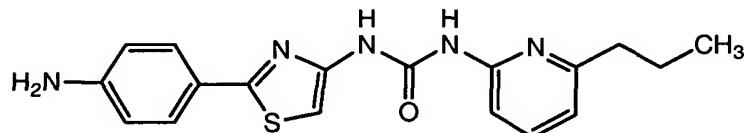


10 1-[2-[4-(4-Morpholinylsulfonyl)phenyl]thiazol-4-yl]-3-(6-propyl-pyridin-2-yl)urea

EI-MS m/z 488.7 (M+H). Calc'd for C₂₂H₂₅N₅O₄S₂: 487.13.

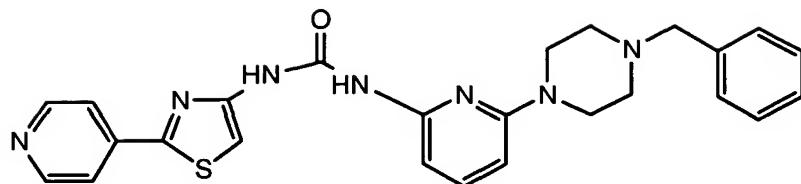
15

Example 128



20 1-[2-(4-Aminophenyl)thiazol-4-yl]-3-(6-propylpyridin-2-yl)urea

EI-MS m/z 354.4 (M+H). Calc'd for C₁₈H₁₉N₅OS: 353.13.

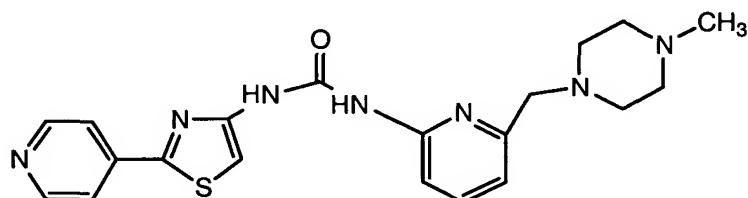
Example 129

5

1-[6-(4-Benzylpiperazin-1-yl)pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea

EI-MS m/z 472.5 (M+H). Calc'd for C₂₅H₂₅N₇OS: 471.18.

10

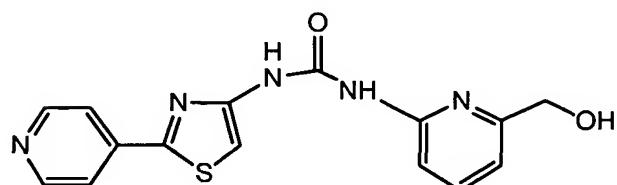
Example 130

15

1-[6-(4-Methyl-piperazin-1-ylmethyl)pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

EI-MS m/z 410.5 (M+H). Calc'd for C₂₀H₂₃N₇OS: 409.17.

20

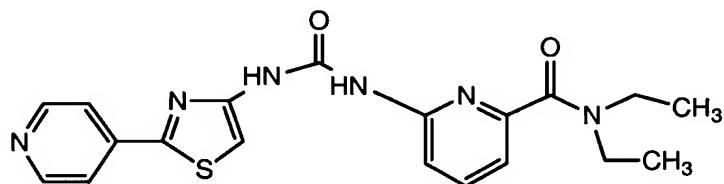
Example 131

1-(6-Hydroxymethyl-pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

EI-MS m/z 328.4 (M+H). Calc'd for C₁₅H₁₃N₅O₂S: 327.08.

5

Example 132

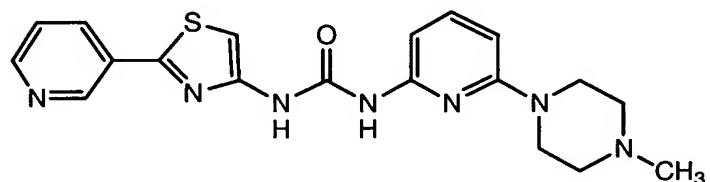


10 **Diethyl 6-[3-(2-pyridin-4-yl-thiazol-4-yl)ureido]-pyridine-2-carboxamide**

EI-MS m/z 397.6 (M+H). Calc'd for C₁₉H₂₀N₆O₂S: 396.14.

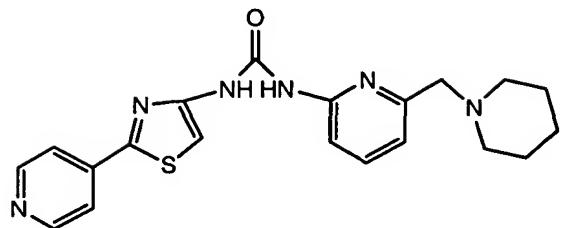
15

Example 133



20 **1-[6-(4-Methylpiperazin-1-yl)pyridin-2-yl]-3-(2-pyridin-3-yl-thiazol-4-yl)urea**

EI-MS m/z 396.5 (M+H). Calc'd for C₁₉H₂₁N₇OS: 395.15.

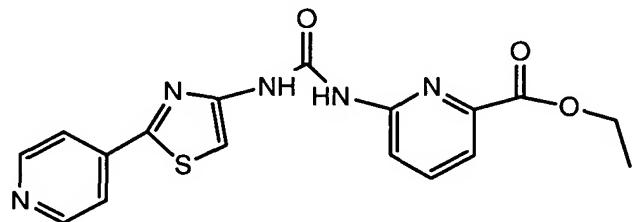
Example 134

5

1-(6-Piperidin-1-ylmethyl-pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

EI-MS m/z 395.6 (M+H). Calc'd for C₂₀H₂₂N₆OS: 394.16.

10

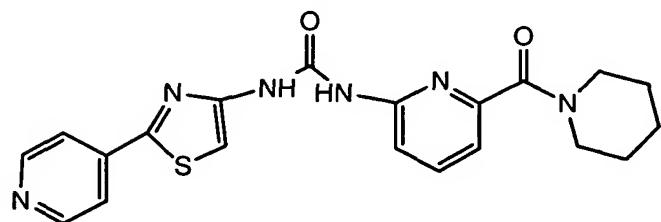
Example 135

15

6-[3-(2-Pyridin-4-yl-thiazol-4-yl)-ureido]-pyridine-2-carboxylic acid ethyl ester

EI-MS m/z 370.4 (M+H). Calc'd for C₁₇H₁₅N₅O₃S: 369.09.

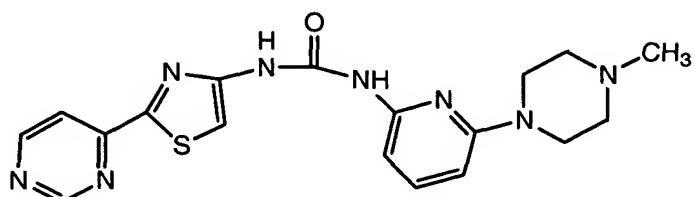
20

Example 136

1-[6-(Piperidine-1-carbonyl)pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea

5 EI-MS m/z 409.5 (M+H). Calc'd for $C_{20}H_{20}N_6O_2S$: 408.14.

Example 137



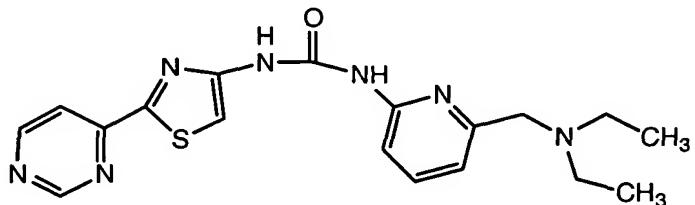
10

1-[6-(4-Methylpiperazin-1-yl)pyridin-2-yl]-3-(2-pyrimidin-4-yl-thiazol-4-yl)urea

EI-MS m/z 397.5 (M+H). Calc'd for $C_{18}H_{20}N_8OS$: 396.15.

15

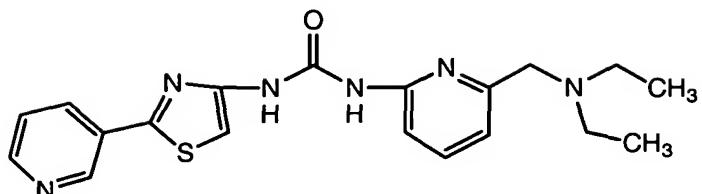
Example 138



20 **1-(6-Diethylaminomethyl-pyridin-2-yl)-3-(2-pyrimidin-4-yl-thiazol-4-yl)urea**

EI-MS m/z 384.6 (M+H). Calc'd for $C_{18}H_{21}N_7OS$: 383.15.

Example 139



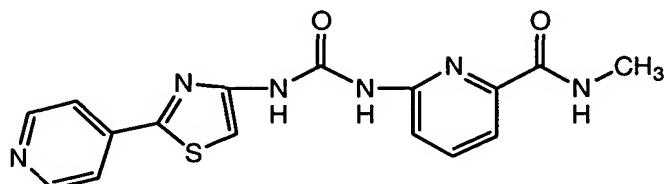
5

1-(6-Diethylaminomethyl-pyridin-2-yl)-3-(2-pyridin-3-yl-thiazol-4-yl)urea

EI-MS m/z 383.5 (M+H). Calc'd for C₁₉H₂₂N₆OS: 382.16.

10

Example 140

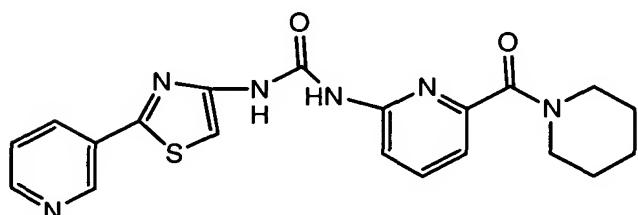


15 Methyl 6-[3-(2-pyridin-4-yl-thiazol-4-yl)ureido]pyridine-2-carboxamide

EI-MS m/z 355.3 (M+H). Calc'd for C₁₆H₁₄N₆O₂S: 354.09.

20

Example 141

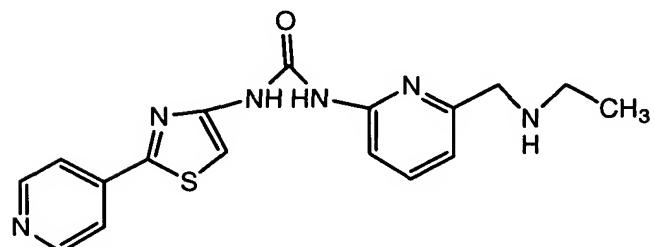


1-[6-(Piperidin-1-carbonyl)pyridin-2-yl]-3-(2-pyridin-3-yl-thiazol-4-yl)urea

EI-MS m/z 409.5 (M+H). Calc'd for C₂₀H₂₀N₆O₂S: 408.14.

5

Example 142

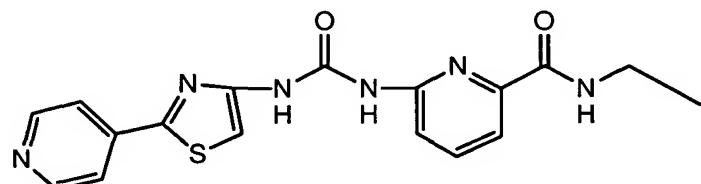


10 **1-(6-Ethylaminomethylpyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)urea**

EI-MS m/z 355.5 (M+H). Calc'd for C₁₇H₁₈N₆OS: 354.13.

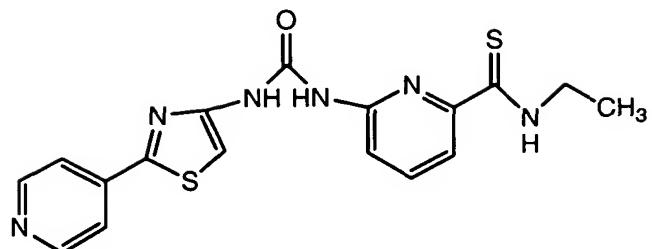
15

Example 143



20 **Ethyl 6-[3-(2-Pyridin-4-yl-thiazol-4-yl)ureido]pyridine-2-carboxamide**

EI-MS m/z 369.4 (M+H). Calc'd for C₁₇H₁₆N₆O₂S: 368.11.

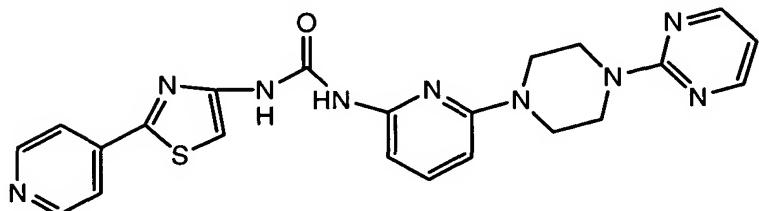
Example 144

5

Ethyl 6-[3-(2-pyridin-4-yl-thiazol-4-yl)ureido]-pyridine-2-thiocarboxamide

EI-MS m/z 385.5 (M+H). Calc'd for C₁₇H₁₆N₆OS₂: 384.08.

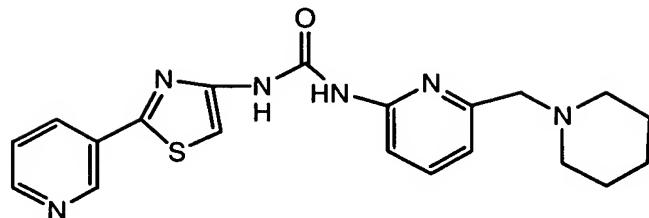
10

Example 145

15

1-(2-Pyridin-4-yl-thiazol-4-yl)-3-[6-(4-pyrimidin-2-yl-piperazin-1-yl)pyridin-2-yl]urea

EI-MS m/z 460.5 (M+H). Calc'd for C₂₂H₂₁N₉OS: 459.16.

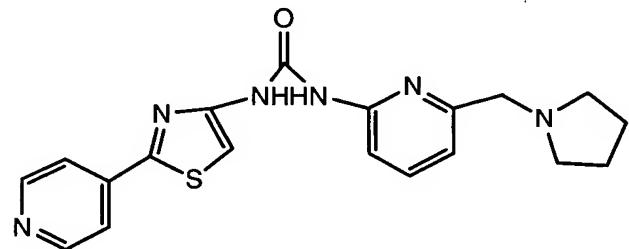
Example 146

5

1-(6-Piperidin-1-ylmethyl-pyridin-2-yl)-3-(2-pyridin-3-yl-thiazol-4-yl)-urea

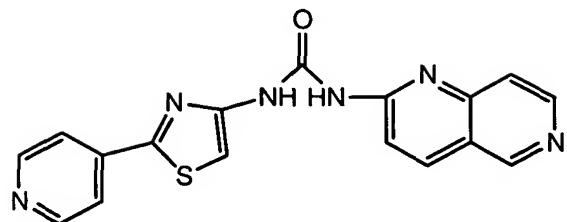
EI-MS m/z 395.5 (M+H). Calc'd for C₂₀H₂₂N₆OS: 394.16.

10

Example 147

15 **1-(2-Pyridin-4-yl-thiazol-4-yl)-3-(6-pyrrolidin-1-ylmethyl-pyridin-2-yl)-urea**

EI-MS m/z 381.5 (M+H). Calc'd for C₁₉H₂₀N₆OS: 380.14.

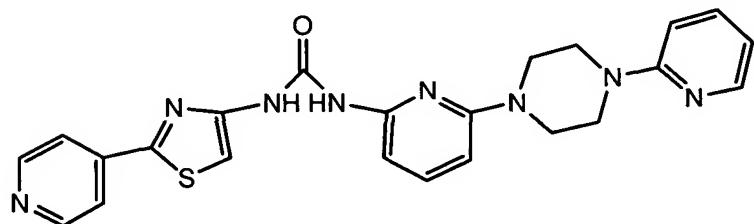
Example 148

5

1-[1,6]Naphthyridin-2-yl-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

EI-MS m/z 349.5 (M+H). Calc'd for C₁₇H₁₂N₆OS: 348.08.

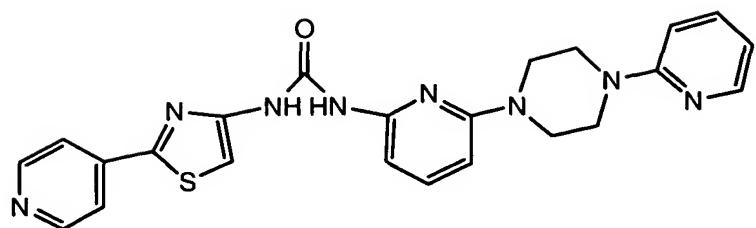
10

Example 149

15

1-[6-(4-Pyridin-2-yl-piperazin-1-yl)pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea

EI-MS m/z 459.5 (M+H). Calc'd for C₂₃H₂₂N₈OS: 458.16.

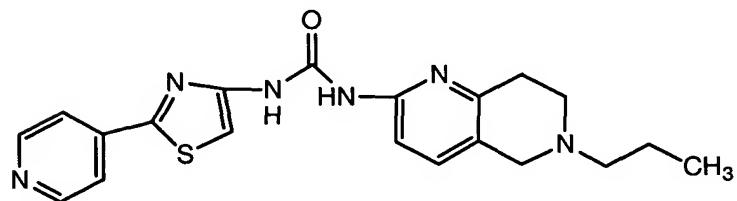
Example 150

5

1-[6-(4-Pyridin-2-yl-piperazin-1-yl)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

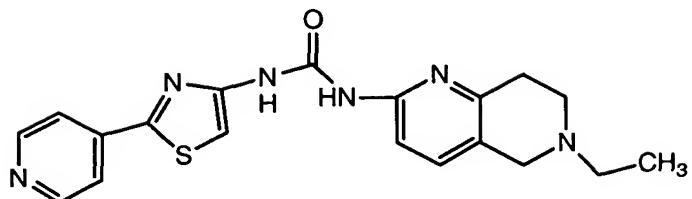
EI-MS m/z 459.5 (M+H). Calc'd for C₂₃H₂₂N₈OS: 458.16.

10

Example 151

15 **1-(6-Propyl-5,6,7,8-tetrahydro-[1,6]naphthyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)-urea**

EI-MS m/z 395.6 (M+H). Calc'd for C₂₀H₂₂N₆OS: 394.16.

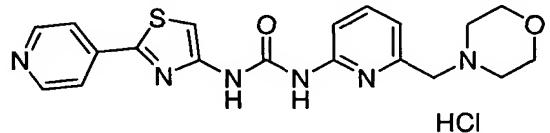
Example 152

5

1-(6-Ethyl-5,6,7,8-tetrahydro-[1,6]naphthyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

EI-MS m/z 381.5 (M+H). Calc'd for C₁₉H₂₀N₆OS: 380.14.

10

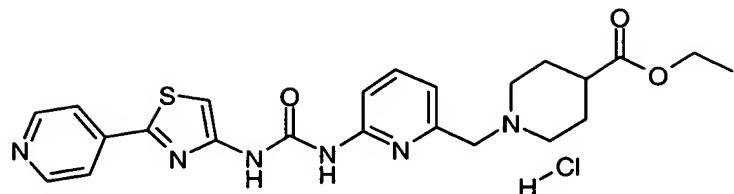
Example 153

15

N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-[6-(1-morpholinylmethyl)pyridinyl]urea hydrochloride

To a solution of N-[2-(pyridin-4-yl)-4-thiazolyl]-N'-2-(6-morpholinylmethylpyridinyl)urea (90 mg, 0.23 mmol, 20 Example 60) in MeOH (3 mL) was added HCl (0.25 mL, 0.25 mmol, 1.0 M in Et₂O). The resulting mixture was stirred at RT for 2 h then concentrated *in vacuo* to give a pale yellow solid.

25 The following Examples 154-165 were prepared from the corresponding amines in a manner similar to that described above for Example 153.

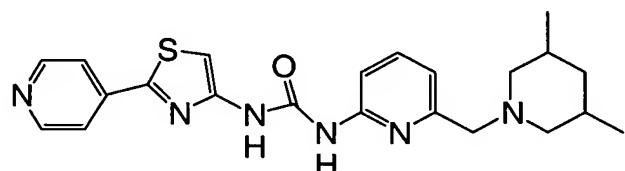
Example 154

5

Ethyl 1-{6-[3-(2-pyridin-4-yl-thiazol-4-yl)ureido]-pyridin-2-ylmethyl}-piperidine-4-carboxylate hydrochloride

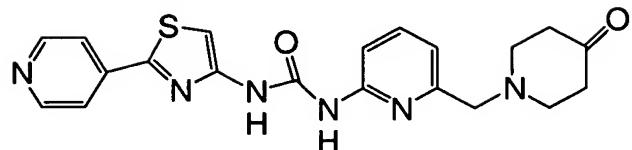
10 Ethyl 1-{6-[3-(2-pyridin-4-yl-thiazol-4-yl)-ureido]-pyridin-2-ylmethyl}-piperidine-4-carboxylate (50 mg, 0.05 mmol, Example 61) in MeOH (5 mL) was treated with HCl (0.12 mL, 0.06 mmol, 1M in Et₂O) to afford the title salt as a yellow solid.

15

Example 155

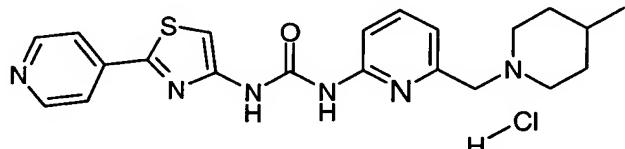
20 1-[6-(3,5-Dimethylpiperidin-1-ylmethyl)pyridin-2-yl]-3-(2-pyridin-4-ylthiazol-4-yl)urea hydrochloride

25 1-[6-(3,5-Dimethylpiperidin-1-ylmethyl)pyridin-2-yl]-3-(2-pyridin-4-ylthiazol-4-yl)urea (52 mg, 0.123 mmol, Example 64) was treated with HCl (0.08 mL, 0.135 mmol, 1 M in Et₂O) to afford the title salt as a yellow solid.

Example 156

5 **1-[6-(4-Oxo-piperidin-1-ylmethyl)pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea hydrochloride**

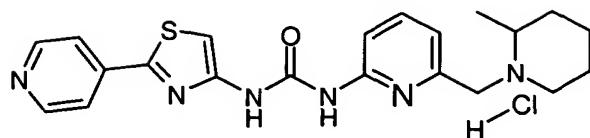
10 1-[6-(4-Oxo-piperidin-1-ylmethyl)pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea (30 mg, 0.073 mmol, Example 175) was treated with HCl (0.08 mL, 0.081 mmol, 1M in Et₂O) to afford the title salt as a yellow solid.

Example 157

15

1-[6-(4-Methylpiperidin-1-ylmethyl)pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea hydrochloride

20 1-[6-(4-Methylpiperidin-1-ylmethyl)pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea (70 mg, 0.171 mmol, Example 65) was treated with HCl (0.19 mL, 0.188 mmol, 1M in Et₂O) to afford the title salt as a yellow solid.

Example 158

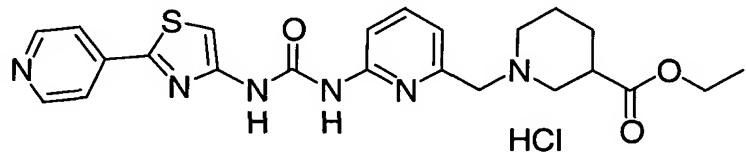
5

1-[6-(2-Methylpiperidin-1-ylmethyl)pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea hydrochloride

10 1-[6-(2-Methylpiperidin-1-ylmethyl)pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea (70 mg, 0.171 mmol, Example 66) was treated with HCl (0.19 mL, 0.188 mmol, 1M in Et₂O) to afford the title salt as a yellow solid.

Example 159

15

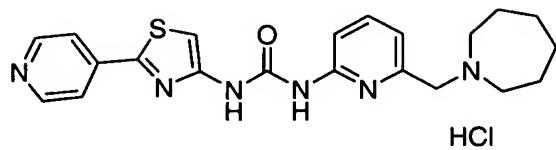


Ethyl 1-{6-[3-(2-pyridin-4-yl-thiazol-4-yl)ureido]-pyridin-2-ylmethyl}piperidine-3-carboxylate hydrochloride

20

20 HCl (0.21 mL, 0.212 mmol, 1.0 M soln in Et₂O) was added to ethyl 1-{6-[3-(2-pyridin-4-yl-thiazol-4-yl)ureido]-pyridin-2-ylmethyl}piperidine-3-carboxylate (90 mg, 0.193 mmol, Example 73) in a solution of MeOH (2 mL) to give a pale yellow solid.

25

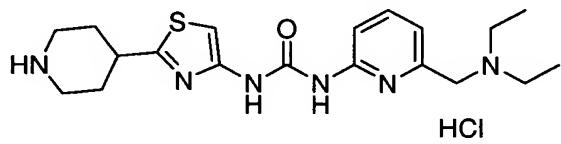
Example 160

5

1-(6-Azepan-1-ylmethyl-pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)urea hydrochloride

HCl (0.29 mL, 0.28 mmol, 1.0 M soln in Et₂O) was added
 10 to 1-(6-azepan-1-ylmethyl-pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)urea (106 mg, 0.26 mmol, Example 71) in a solution of MeOH (4 mL) and the resulting mixture stirred 6 h. Concentration *in vacuo* gave a yellow solid.

15

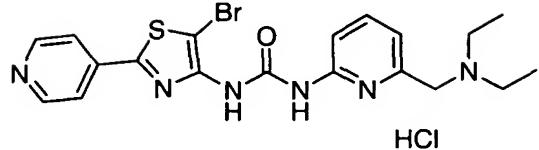
Example 161

1-(6-Diethylaminomethyl-pyridin-2-yl)-3-(2-piperidin-4-yl-thiazol-4-yl)urea hydrochloride

HCl (27 μ L, 0.026 mmol, 1.0 M soln in Et₂O) was added
 20 to 1-(6-diethylaminomethyl-pyridin-2-yl)-3-(2-piperidin-4-yl-thiazol-4-yl)urea (11 mg, 0.026 mmol, Example 179) in a solution of MeOH (1 mL) and the resulting mixture stirred 3 h. Concentration *in vacuo* gave a yellow solid.

Example 162

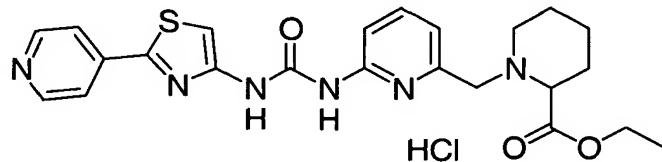
5



1-[5-Bromo-2-(pyridin-4-yl)thiazol-4-yl]-3-(6-diethylaminomethyl-pyridin-2-yl)urea hydrochloride

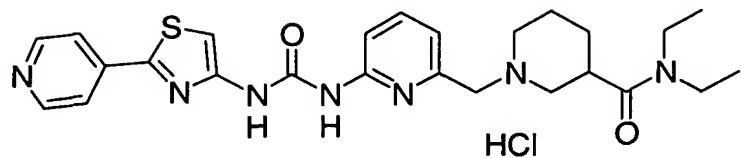
10 HCl (54 mL, 0.054 mmol, 1.0 M soln in Et₂O) was added to 1-[5-bromo-2-(pyridin-4-yl)thiazol-4-yl]-3-(6-diethylaminomethyl-pyridin-2-yl)urea (25 mg, 0.054 mmol, Example 180) in a solution of MeOH (0.5 mL) to give a yellow solid.

15

Example 163

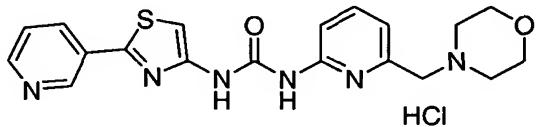
20 **Ethyl 1-{6-[3-(2-pyridin-4-yl-thiazol-4-yl)-ureido]-pyridin-2-ylmethyl}-piperidine-2-carboxylate hydrochloride**

25 HCl (0.12 mL, 0.12 mmol, 1.0 M soln in Et₂O) was added to ethyl 1-{6-[3-(2-pyridin-4-yl)thiazol-4-yl]ureido}-pyridin-2-ylmethyl)piperidine-2-carboxylate (50 mg, 0.11 mmol, Example 74) in a solution of MeOH (2 mL) to give a pale yellow solid.

Example 164

5 **N,N-Diethyl 1-{6-[3-(2-pyridin-4-yl-thiazol-4-yl)-ureido]pyridin-2-ylmethyl}piperidine-3-carboxamide hydrochloride**

10 HCl (0.15 mL, 0.156 mmol, 1.0 M soln in Et₂O) was added to N,N-diethyl 1-{6-[3-(2-pyridin-4-yl-thiazol-4-yl)-ureido]pyridin-2-ylmethyl}piperidine-3-carboxamide (70 mg, 0.142 mmol, Example 75) in a solution of MeOH (3 mL) to give a pale yellow solid.

15 Example 165

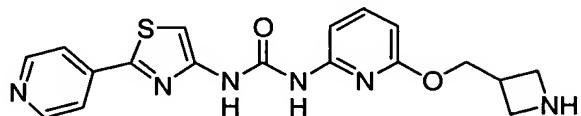
20 1-[6-(Morpholin-4-ylmethyl)-pyridin-2-yl]-3-[(2-pyridin-3-yl)thiazol-4-yl]urea hydrochloride

25 HCl (55 mL, 0.05 mmol, 1.0 M in Et₂O) was added to 1-[6-(morpholin-4-ylmethyl)-pyridin-2-yl]-3-[(2-pyridin-3-yl)thiazol-4-yl]urea (20 mg, 0.05 mmol, Example 180) in a solution of MeOH (1 mL) and the resulting mixture stirred 3 h. Concentration *in vacuo* gave a yellow solid.

The following Examples 166-167 were prepared from the corresponding protected amines in a manner similar to that described above for Example 157:

5

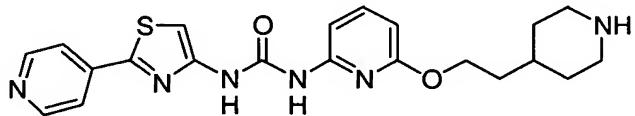
Example 166



10 1-[6-(Azetidin-3-ylmethoxy)pyridin-2-yl]-3-[2-(pyridin-4-yl)thiazol-4-yl]urea

15 From *tert* butyl 3-{6-[3-(2-pyridin-4-yl-thiazol-4-yl)-ureido]-pyridin-2-yloxy-methyl}-azetidine-1-carboxylate
(Example 80) EI-MS *m/z* 382.2 (M+H). Calc'd for C₁₈H₁₈N₆O₂S: 382.12.

Example 167

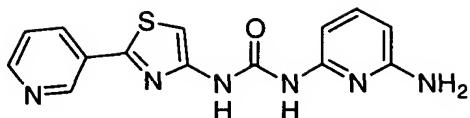


20 1-[6-(2-Piperidin-4-yl-ethoxy)pyridin-2-yl]-3-[2-(pyridin-4-yl)thiazol-4-yl]urea

25 From *tert*-butyl 4-(2-{6-[3-(2-pyridin-4-yl-thiazol-4-yl)ureido]pyridin-2-yloxy}ethyl)piperidine-1-carboxylate
(Example 81) MS *m/z*: 425 (M+1)⁺. Calc'd for C₂₁H₂₄N₆O₂S: 424.17.

Example 168

30



N-[2-(3-Pyridinyl)-4-thiazolyl]-N'-2-[6-aminopyridin-2-yl]urea

5

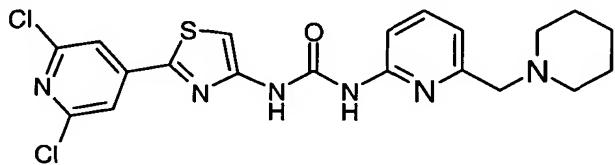
TEA (0.27 mL, 1.94 mmol) was added to a solution of 2-(pyridin-3-yl)thiazole-4-carboxylic acid (200 mg, 0.97 mmol) and 4A molecular sieves in THF (25 mL) under N₂ at RT.

(PhO)₂PON₃ (0.33 mL, 1.55 mmol) followed by 2,6-diaminopyridine (265 mg, 2.43 mmol) was added and the resulting mixture was heated at reflux for 12 h. After cooling to RT, the heterogeneous mixture was decanted to remove the molecular sieves. The precipitate was collected, rinsing with EtOAc to give a light tan solid. MS m/z: 313.0 (M+H). Calc'd for C₁₄H₁₂N₆OS: 312.08.

The following compounds were prepared from the corresponding amines in a manner similar to that described above for Example 168:

20

Example 169



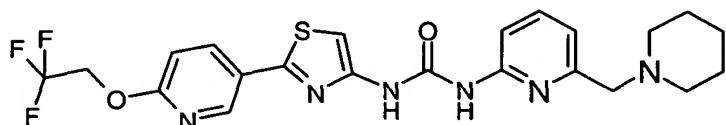
25 **1-[2-(2,6-Dichloropyridin-4-yl)thiazol-4-yl]-3-[6-(piperidin-1-ylmethyl)pyridin-2-yl]urea**

2-(2,6-Dichloropyridin-4-yl)thiazol-4-carboxylic acid (100 mg, 0.36 mmol), 2-amino-6-piperidinylmethyl-pyridine

(76 mg, 0.39 mmol), $(\text{PhO})_2\text{PON}_3$ (0.1 mL, 0.55 mmol), and TEA (0.08 mL, 0.55 mmol) were heated in toluene (15 mL) to yield the title compound as white solid. MS m/z : 464.3 (M+H). Calc'd. for $\text{C}_{20}\text{H}_{20}\text{Cl}_2\text{N}_6\text{OS}$ - 463.39.

5

Example 170

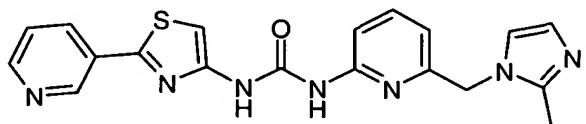


10 1-[6-(Piperidin-1-ylmethyl)pyridin-2-yl]-3-[2-[6-(2,2,2-trifluoroethoxy)pyridin-3-yl]thiazol-4-yl]urea

15 2-(4-Trifluoroethoxy)pyridin-4-yl thiazolyl-4-carboxylic acid (150 mg, 0.49 mmol), 2-amino-6-piperidinylmethyl-pyridine (104 mg, 0.54 mmol), $(\text{PhO})_2\text{PON}_3$ (0.16 mL, 0.74 mmol), and TEA (0.1 mL, 0.74 mmol) were heated in toluene (15 mL) to yield the title compound as white solid. MS m/z : 493.6 (M+H). Calc'd. for $\text{C}_{22}\text{H}_{23}\text{F}_3\text{N}_6\text{O}_2\text{S}$ - 492.52.

20

Example 171



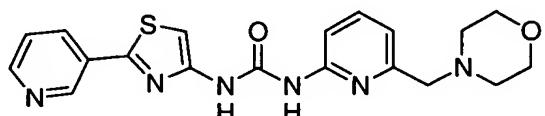
25 1-[6-(2-Methylimidazol-1-ylmethyl)pyridin-2-yl]-3-(pyridin-3-yl)thiazol-4-yl]urea

2-(Pyridin-3-yl)-4-thiazole-4-carboxylic acid (75 mg, 0.36 mmol), 2-amino-6-[2-methylimidazol-1-yl]methyl-pyridine

(75 mg, 0.40 mmol), $(\text{PhO})_2\text{PON}_3$ (0.12 mL, 0.54 mmol), and TEA (0.1 mL, 0.54 mmol) were heated in toluene (15 mL) to yield the title compound as light brown solid. MS m/z : 392.3 (M+H). Calc'd. for $\text{C}_{19}\text{H}_{17}\text{N}_7\text{OS}$ - 391.45.

5

Example 172

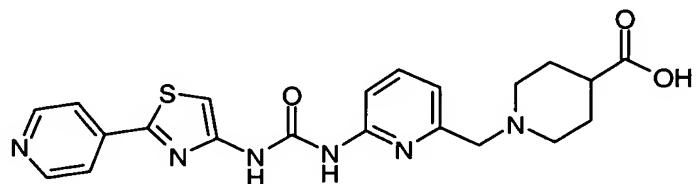


10 **1-[6-(Morpholin-4-ylmethyl)-pyridin-2-yl]-3-[(2-pyridin-3-yl)thiazol-4-yl]urea**

TEA (0.27 mL, 1.94 mmol) was added to a solution of 2-(pyridin-3-yl)thiazole-4-carboxylic acid (200 mg, 0.97 mmol) 15 and 4A molecular sieves in THF (25 mL) under N_2 at RT. $(\text{PhO})_2\text{PON}_3$ (0.33 mL, 1.55 mmol) followed by 2-amino, 6-morpholinylmethylpyridine (280 mg, 1.45 mmol) was added and the resulting mixture was heated at reflux for 12 h. After cooling to RT, the heterogeneous mixture was decanted to 20 remove the molecular sieves. The precipitate was collected, rinsed with EtOAc and purified by chromatography on silica gel ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 95:5) to give a white solid. MS m/z : 397.1 (M+H). Calc'd for $\text{C}_{19}\text{H}_{20}\text{N}_6\text{O}_2\text{S}$ - 396.47.

25

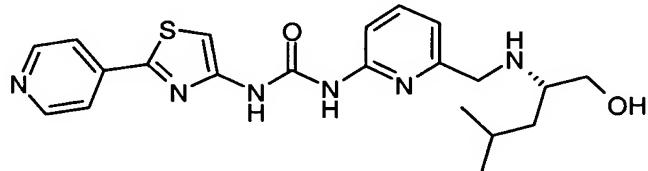
Example 173



1-{6-[3-(2-(4-Pyridinyl)-4-thiazolyl)ureido]-pyridin-2-ylmethyl}-piperidine-4-carboxylic acid

Ethyl 1-{6-[3-(2-(pyridin-4-yl)thiazol-4-yl)ureido]-pyridin-2-ylmethyl}-piperidine-4-carboxylate (55 mg, 0.12 mmol, Example 61) was suspended in MeOH (10 ml) followed by adding LiOH (50 mg, 1.18 mmol) in H₂O (1 ml). The resulting mixture was heated at 45°C for 15 h. After cooling to RT, the solvent was removed. The residue was suspended in H₂O (20 mL). The pH was adjusted to 7 using HCl (1N). The resulting mixture was extracted with CHCl₃:iPrOH (3:1). The organic layer was washed with H₂O and brine. After being dried over anhydrous MgSO₄, the solvent was removed *in vacuo* to yield the final compound as light yellow solid. MS *m/z*: 438.7 (M+H). Calc'd. for C₂₁H₂₂N₆O₃S - 438.51.

Example 174



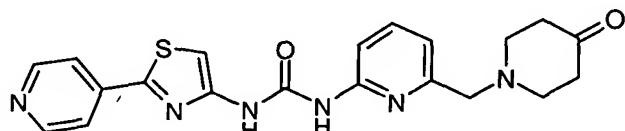
20 **1-{6-[(1-Hydroxymethyl-3-methylbutylamino)methyl]-pyridin-2-yl}-3-(2-pyridin-4-yl-thiazol-4-yl)urea**

25 *tert*-Butyl (1-hydroxymethyl-3-methyl-butyl)-{6-[3-(2-pyridin-4-yl-thiazol-4-yl)-ureido]-pyridin-2-ylmethyl}-carbamate (165 mg, 0.313 mmol, Example 62) in MeOH (5 mL) was treated with HCl (0.16 mL, 0.627 mmol, 4M in dioxane). The resulting stirred solution was heated at 40°C in a closed system for 15 h. After cooling to RT, the pH was 30 adjusted to 7 using 1 N NaOH. Solvent was removed and the residue was extracted with CHCl₃. The organic layer was

washed with H_2O , brine, dried over $MgSO_4$, and concentrated to yield a brown liquid crude product. This crude product was purified by chromatography on silica gel. Elution with $CH_2Cl_2:MeOH$ mixture (95:5) gave the final compound as a tan 5 solid. MS m/z : 427.2 (M+H). Calc'd. for $C_{21}H_{26}N_6O_2S$ - 426.54.

Example 175

10



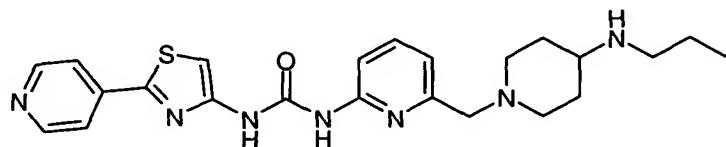
1-[6-(4-Oxo-piperidin-1-ylmethyl)pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea

15

N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-[6-(4-ethoxyacetal)piperidylmethyl]urea (300 mg, 0.66 mmol) in THF (15 mL) was treated with 5N HCl (5 mL). The resulting mixture was heated to reflux under N_2 for 5 h. After cooling to RT, the mixture was basified using 5 N NaOH. 20 Solvent was removed and the residue was extracted with $CHCl_3$. The organic layer was washed with H_2O , brine, dried over $MgSO_4$, and concentrated to yield a pale yellow solid. MS m/z : 409.3 (M+H). Calc'd. for $C_{20}H_{20}N_6O_2S$ - 408.32.

25

Example 176

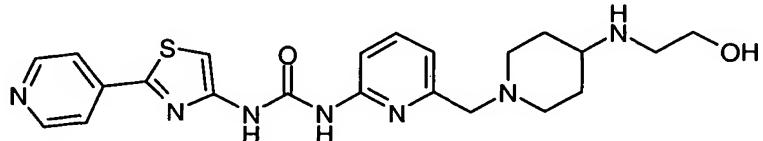


1-[6-[4-(Propylamino)piperidin-1-ylmethyl]pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea

To a suspension of N-[2-(4-pyridinyl)-4-thiazolyl]-N'-2-[6-(piperidin-4-yl)methyl]urea (50 mg, 0.12 mmol, Example 175) in MeOH (10 mL) was added propylamine (0.1 mL, 1.22 mmol). The resulting mixture was heated at 50°C for 4 h under N₂. After the mixture was cooled to RT, NaBH₄ (83 mg, 2.20 mmol) was added. The mixture was stirred at RT under N₂ for 3 h. Solvent was removed *in vacuo* and the crude product was purified by chromatography on silica gel. Elution with CH₂Cl₂:MeOH (90:10) gave the title compound as a white solid. MS *m/z*: 451.7 (M+H). Calc'd. for C₂₃H₂₉N₇OS - 451.6.

15

Example 177

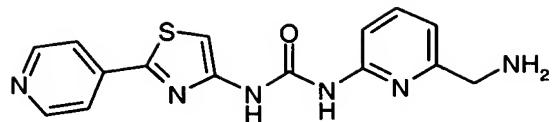


20 **1-[6-[4-(2-Hydroxyethylamino)piperidin-1-ylmethyl]-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea**

N-[2-(4-Pyridinyl)-4-thiazolyl]-N'-2-[6-(piperidin-4-yl)methyl]urea (60 mg, 0.147 mmol, Example 175) and 25 ethanolamine (0.09 mL, 1.47 mmol) were heated in MeOH (10 mL) yielded the title compound as pale yellow solid. MS *m/z*: 454.6 (M+H). Calc'd. for C₂₂H₂₇N₇O₂S - 453.57.

Example 178

30



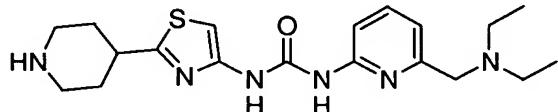
N-(6-Aminomethyl-2-pyridyl)-N'-(2-(4-pyridinyl)-4-thiazolyl)urea

5

Pd(OH)₂ (70 mg, 0.5 mmol) was suspended in EtOH (5 mL) followed by adding N-(6-azidomethyl-2-pyridyl)-N'-(2-(4-pyridinyl)-4-thiazolyl)urea (70 mg, 0.198 mmol, Example 69) in EtOH (8 mL). The resulting mixture was heated at 45°C under H₂ balloon for 3 h. After cooling to RT, the mixture was filtered by passing through 2 layers of pleated filtered papers. Solvent was removed *in vacuo* to yield the final compound as a yellow solid. MS *m/z*: 327.3 (M+H). Calc'd. for C₁₅H₁₄N₆OS - 326.38.

15

Example 179



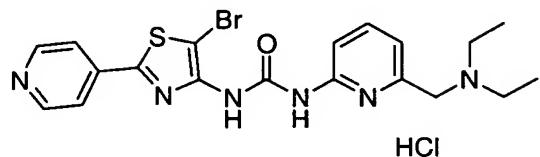
20 **1-(6-Diethylaminomethyl-pyridin-2-yl)-3-(2-piperidin-4-yl)-4-thiazolylurea**

Lithium triethylborohydride (0.84 mL, 0.84 mmol, 1.0 M in THF) was added to a solution of 1-(6-diethylamino-methyl-pyridin-2-yl)-3-(2-piperidin-4-yl-thiazol-4-yl)urea (100 mg, 0.24 mmol, Example 117) and DIEA (63 μ L, 0.36 mmol) in THF (5 mL) and the resulting mixture was stirred 6 h at RT. The reaction was quenched via dropwise addition of MeOH and concentrated *in vacuo*. Purification by preparative HPLC (5-

60% CH₃CN/H₂O) gave a white solid. MS *m/z*: 389.2 (M+H).
Calc'd for C₁₉H₂₈N₆OS - 388.53.

Example 180

5



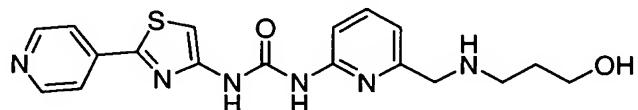
1-[5-Bromo-2-(pyridin-4-yl)thiazol-4-yl]-3-(6-diethylaminomethyl-pyridin-2-yl)urea

10

Bromine (46 μ L, 0.90 mmol) was added to a solution of 1-(6-diethylaminomethyl-pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)urea (190 mg, 0.45 mmol, Example 117) in MeOH (8 mL) and the resulting solution was stirred at RT for 1 h. 15 The reaction was quenched with saturated sodium bisulfite solution and concentrated *in vacuo*. The residue was dissolved in CHCl₃/IpOH (3/1, 10 mL) and washed with H₂O (3x10 mL) followed by 1N NaOH solution (10 mL). The organics were combined, dried over Na₂SO₄, and concentrated 20 *in vacuo* to give a yellow solid. MS *m/z*: 461.1 (M+H).
Calc'd for C₁₉H₂₁BrN₆OS - 461.39.

Example 181

25



1-{6-[(3-Hydroxypropylamino)methyl]-pyridin-2-yl}-3-(2-pyridin-4-yl-thiazol-4-yl)urea

30 Step A

2-(4-Pyridinyl)-4-thiazolcarbonylazide (220 mg, 0.78 mmol) and 2-amino-6-[N''-tert-butoxycarbonyl-N''-3-hydroxypropyl]amino]methylpyridine (196 mg, 0.94 mmol) in dry toluene (10 mL) were heated at 100°C for 12 h to give a pale yellow solid which was purified by chromatography on silica gel (CH₂Cl₂/MeOH, 95:5) to give N-[2-(pyridin-4-yl)-4-thiazolyl]-N'-2-[6-(N''-tert-butoxycarbonyl-N''-(3-hydroxypropyl)-amino)methyl]pyridinyl urea as a white solid. MS *m/z*: 485.2 (M+H). Calc'd for C₂₃H₂₈N₆O₄S - 484.58.

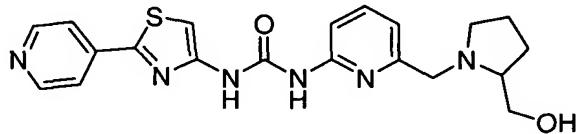
10

Step B

HCl (112 μ L, 0.112 mmol, 1.0 M in Et₂O) was added to a solution of N-[2-(pyridin-4-yl)-4-thiazolyl]-N'-2-[6-(N''-tert-butoxycarbonyl-N''-(3-hydroxypropyl)-amino)methyl]pyridinyl urea (25 mg, 0.051 mmol, Step A) in MeOH (1 mL) and the resulting mixture was heated at 45°C for 12 h. A yellow precipitate formed and was filtered off, rinsing with hexane. The precipitate was added to CH₂Cl₂ (15 mL) and washed with 1N NaOH solution (5 mL). The organics were collected, dried over Na₂SO₄ and concentrated *in vacuo* to give a pale yellow solid. MS *m/z*: 385.0 (M+H). Calc'd for C₁₈H₂₀N₆O₂S - 384.62.

Example 182

25



1-[6-(2-Hydroxymethylpyrrolidin-1-ylmethyl)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)urea

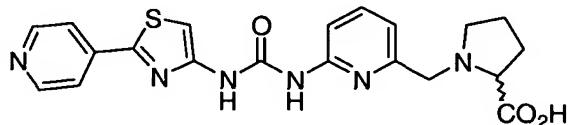
30

LiAlH₄ (3 mg, 0.079 mmol) was added to a solution of methyl 1-[6-(3-(2-pyridin-4-yl-thiazol-4-yl)ureido)-pyridin-

2-ylmethyl}-pyrrolidine-2-carboxylate (15 mg, 0.034 mmol, Example 77) in THF (5 mL) at RT and the resulting mixture was stirred for 8 h. A precipitate formed and was collected. The solid was dissolved in CHCl₃ (5 mL) and 5 washed with saturated NaHCO₃ solution (5 mL). The aqueous layer was adjusted to pH 7 with 1N HCl and extracted with CHCl₃. The organics were combined, dried over MgSO₄ and concentrated *in vacuo* to give a pale yellow solid. MS *m/z*: 411.1 (M+H). Calc'd for C₂₀H₂₂N₆O₂S - 410.50.

10

Example 183

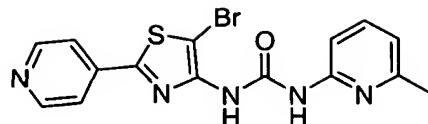


15 1-{6-[3-(2-pyridin-4-yl-thiazol-4-yl)ureido]-pyridin-2-
ylmethyl}-pyrrolidine-2-carboxylic acid

A 1.0 N NaOH solution (0.40 mL) was added to a solution of methyl 1-{6-[3-(2-pyridin-4-yl-thiazol-4-
20 yl)ureido]-pyridin-2-ylmethyl}pyrrolidine-2-carboxylate (3 mg, 6.84 μ M, Example 77) in MeOH (1 mL) and the resulting mixture was stirred at RT for 12 h. The mixture was adjusted to pH 7 with 1N HCl solution and concentrated *in vacuo*. The residue was dissolved in CH₂Cl₂ and a few drops 25 of MeOH. A precipitate formed and was collected to give a white solid. MS *m/z*: 423.5 (M-H) Calc'd for C₂₀H₂₀N₆O₃S - 424.48.

Example 184

30



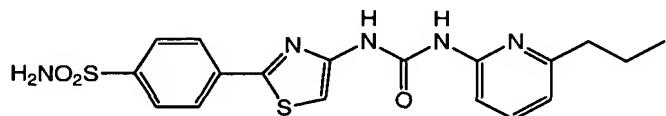
1-(5-Bromo-(2-pyridin-4-yl)thiazol-4-yl)-3-(6-methylpyridin-2-yl)urea

5

NBS (686 mg, 3.85 mmol) and AIBN (158 mg, 0.96 mmol) were added to a heterogeneous solution of 1-((2-pyridin-4-yl)thiazol-4-yl)-3-(6-methylpyridin-2-yl)urea (600 mg, 1.93 mmol, Example 6) in CCl_4 (25 mL) and the resulting mixture 10 was heated at reflux for 2 h. After cooling to RT, a precipitate formed and was collected, rinsing with hexane to give a white solid. MS m/z : 392.0 ($\text{M}+2\text{H}$). Calc'd for $\text{C}_{15}\text{H}_{12}\text{BrN}_5\text{OS}$ - 390.26.

15

Example 185

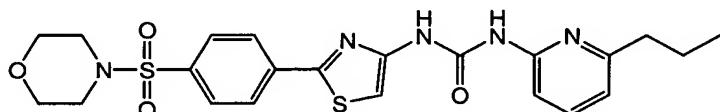


4-{4-[3-(6-Propylpyridin-2-yl)-ureido]-thiazol-2-yl}-benzenesulfonamide

20 In an oven-dried, 50-mL, round-bottomed flask were placed 2-(*p*-sulfamoylphenyl)thiazole-4-carboxylic acid (250 mg, 0.82 mmol), molecular sieves (800 mg) in THF (20 mL). 25 To this mixture was added Et_3N (0.23 mL, 1.64 mmol), followed by DPPA (0.28 mL, 1.28 mmol). The reaction was stirred for 5 min, then 6-propylpyridine-2-amine (280 mg, 2.06 mmol) was added. The suspension was heated to 75°C for 14 h, cooled to RT, diluted with H_2O (10 mL) and EtOAc (150 mL), and filtered to remove molecular sieves. The filtrate 30

was concentrated *in vacuo* to give the crude product as a yellow solid which was filtered, washed with H₂O (3 x 10 mL), EtOAc (1 x 10 mL) and Et₂O (3 x 10 mL) to afford the title compound as a yellow solid. MS m/z: 418 (M+H). Calc'd for C₁₈H₁₉N₅O₃S₂: 417.09.

Example 186



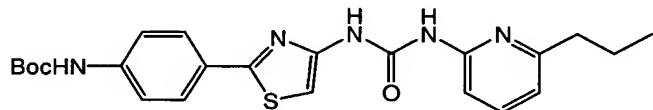
10

1-[2-[(4-Morpholinylsulfonyl)phenyl]thiazol-4-yl]-3-(6-propylpyridin-2-yl)urea

In a manner similar to that described for the preparation of Example 185, 2-[(4-morpholinylsulfonyl)phenyl]thiazole-4-carboxylic acid (354 mg) was treated with DPPA and 6-propylpyridine-2-amine to give the title compound. MS m/z: 488 (M+H). Calc'd for C₂₂H₂₅N₅O₄S₂: 487.13.

20

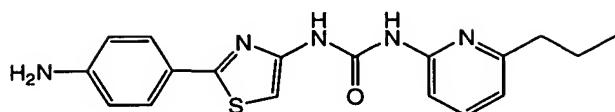
Example 187



25

tert-Butyl (4-[(3-(6-propylpyridin-2-yl)ureido)thiazol-2-yl]phenyl)carbamate

In a manner similar to that described for the preparation of Example 185, 2-[(N-Boc-amino)-phenyl]thiazole-4-carboxylic acid (130 mg) was treated with DPPA and 6-propylpyridine-2-amine to give the title compound. MS m/z: 454.5 (M+H). Calc'd for C₂₃H₂₇N₅O₃S: 453.18.

Example 188

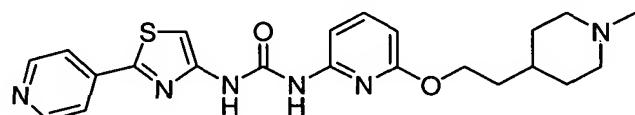
5

1-[2-(4-Aminophenyl)thiazol-4-yl]-3-(6-propylpyridin-2-yl)urea

In an oven-dried, 25-mL, round-bottomed flask were
 10 placed N-[6-propylpyridine]-N'-[4-[N-Bocamino]phenyl]-4-thiazolylurea (55 mg, 0.12 mmol, Example 187), thioanisole (0.35 mL) in CH_2Cl_2 (10 mL). TFA (0.35 mL) was added, the mixture was stirred at RT for 6 h then concentrated *in vacuo*. Purification by flash chromatography on silica gel
 15 [EtOAc/hexane (extracted with aq. NH_4OH), 40:60] afforded the title compound. MS m/z: 354.0 (M+H). Calc'd for $\text{C}_{18}\text{H}_{19}\text{N}_5\text{OS}$: 353.13.

Example 189

20



1-{6-[2-(1-Methylpiperidin-4-yl)ethoxy]pyridin-2-yl}-3-(2-pyridin-4-yl-thiazol-4-yl)urea

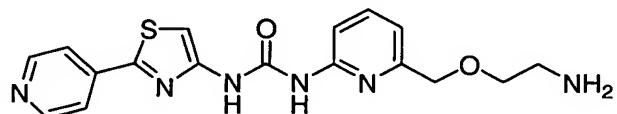
25

A mixture of N-[2-(4-pyridinyl)-4-thiazolyl]-N'-2-[6-(4-piperidinylethoxy)pyridinyl]urea (0.17 g, 0.40 mmol, Example 167), paraformaldehyde (0.17 g), and $\text{NaBH}(\text{OAc})_3$ (0.21 g, 1.0 mmol) in 40 mL of CH_2Cl_2 was stirred at RT under N_2 for 12 h. After 12 h, the solvent was removed *in vacuo*, and the residue was diluted with 20 mL of H_2O , then

extracted with $\text{CHCl}_3/\text{IpOH}$ (3:1, 3X20 mL). The combined organic portions were washed with brine, and dried over MgSO_4 , and the solvents were removed *in vacuo* to yield a residue. Purification over silica gel (gradient, 5% to 7.5% 5 $\text{MeOH}/\text{CH}_2\text{Cl}_2$ with 0.5% of TEA) provided the title compound as an off-white solid. MS *m/z*: 439 (M+H). Calc'd for $\text{C}_{22}\text{H}_{26}\text{N}_6\text{O}_2\text{S}$: 438.18.

Example 190

10



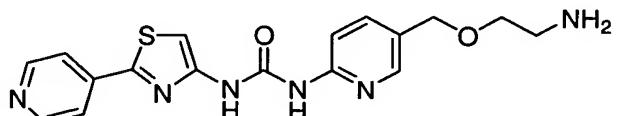
1-[6-(2-Aminoethoxymethyl)pyridin-2-yl]-3-(2-pyridin-4-yl-
thiazol-4-yl)urea

15

Prepared in a manner similar to that described in Example 189. MS *m/z*: 371 (M+H). Calc'd for $\text{C}_{17}\text{H}_{18}\text{N}_6\text{O}_2\text{S}$: 370.12.

20

Example 191

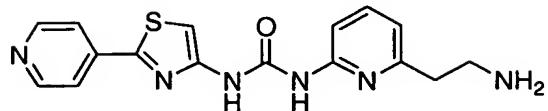


25

1-[5-(2-Aminoethoxymethyl)pyridin-2-yl]-3-(2-pyridin-4-yl-
thiazol-4-yl)urea

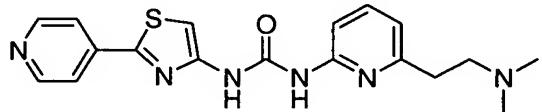
Prepared in a manner similar to that described in Example 189. MS *m/z*: 371 (M+H). Calc'd for $\text{C}_{17}\text{H}_{18}\text{N}_6\text{O}_2\text{S}$: 370.12.

30

Example 192

5 **1-(6-[2-Aminoethyl]pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)urea**

10 To a mixture of 1-{6-[2-(phthalimidyl)ethyl]-pyridin-2-yl}-3-(2-pyridin-4-yl-thiazol-4-yl)urea (75 mg, 0.16 mmol, Example 88) and EtOH (10 mL) was added hydrazine hydrate (0.1 mL, 0.18 mmol). The mixture was heated at reflux for 2 h then cooled to RT. The residue was dissolved in 3:1 CHCl₃/IpOH, washed with saturated NaHCO₃, dried (MgSO₄) and concentrated *in vacuo* to afford the title compound as a yellow solid. MS m/z: 341.0 (M+H). Calc'd for C₁₆H₁₆N₆OS: 340.11.

Example 193

20

1-(6-[2-(N,N-Dimethylamino)ethyl]pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)urea

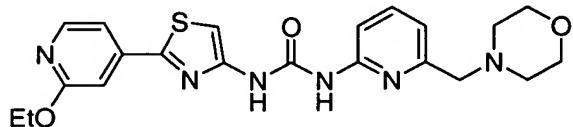
25 To a solution of 1-(6-[2-aminoethyl]pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)urea (20 mg, 0.06 mmol, Example 192) and CH₂Cl₂ (5 mL) was added paraformaldehyde (20 mg) and NaBH(OAc)₃ (30 mg, 0.14 mmol). The mixture was stirred at RT for 2.5 h. Extracted with 3:1 CHCl₃/IpOH and washed with brine, dried (MgSO₄) and concentrated *in vacuo* to

30

afford the desired compound as a yellow solid. MS m/z: 369.1 (M+H). Calc'd for C₁₈H₂₀N₆OS: 368.14.

Example 194

5



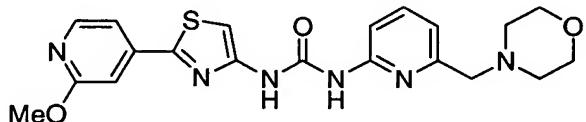
1-[2-(2-Ethoxypyridin-4-yl)thiazol-4-yl]-3-(6-morpholin-4-ylmethyl-pyridin-2-yl)urea

10

To a mixture of 1-[2-(2-chloropyridin-4-yl)thiazol-4-yl]-3-(6-morpholin-4-ylmethyl-pyridin-2-yl)urea (100 mg, 0.23 mmol, Example 90) and EtOH (50 mL) was added a 21 wt% NaOEt/EtOH solution (0.4 mL, 1.2 mmol) and DMF (2 mL). The mixture was heated to reflux for 15 h then additional 21 wt% NaOEt/EtOH solution (10 mL) were added. After 2.5 h, the reaction was complete as judged by LC/MS. The reaction mixture was concentrated *in vacuo* then diluted with EtOAc and the solid was filtered off. The filtrate was concentrated *in vacuo* to afford an orange slushy oil which was purified by silica flash chromatography (5-10% MeOH/CH₂Cl₂) to afford the title compound as a yellow solid. MS m/z: 441.1 (M+H). Calc'd for C₂₁H₂₄N₆O₃S: 440.16.

25

Example 195

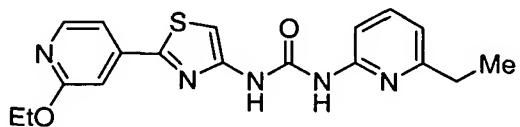


30

1-[2-(2-Methoxypyridin-4-yl)thiazol-4-yl]-3-(6-morpholin-4-ylmethyl-pyridin-2-yl)urea

To a mixture of 1-[2-(2-chloropyridin-4-yl)thiazol-4-yl]-3-(6-morpholin-4-ylmethyl-pyridin-2-yl)urea (100 mg, 0.23 mmol, Example 90) and MeOH (50 mL) was added solid 5 NaOMe (1.6 g, 29.6 mmol) and DMF (20 mL). The reaction mixture was heated to 130°C. After 2 h, the reaction mixture was cooled to RT and filtered. The filtrate was concentrated *in vacuo* and diluted with EtOAc and filtered to remove the solid. The filtrate was concentrated *in vacuo* to 10 afford an orange oil which was purified by silica flash chromatography (5% MeOH/CH₂Cl₂) to afford the title compound as a white solid. MS m/z: 427.2 (M+H). Calc'd for C₂₀H₂₂N₆O₃S: 426.15.

15

Example 196

20

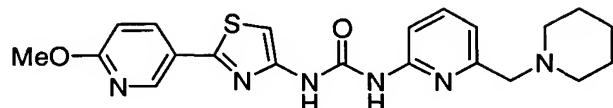
1-[2-(2-Ethoxypyridin-4-yl)thiazol-4-yl]-3-(6-ethyl-pyridin-2-yl)urea

To a 10 mL round bottom flask containing 1-[2-(2-chloropyridin-4-yl)thiazol-4-yl]-3-(6-ethylpyridin-2-yl)urea (40 mg, 0.11 mmol) (prepared similar to that described for 25 Example 95) was charged a 21 wt% NaOEt/EtOH solution (5 mL). The reaction mixture was heated to reflux. After 2 h, the reaction mixture was cooled to RT and diluted with H₂O then concentrated *in vacuo*. The solid residue was washed with CH₂Cl₂ and EtOAc then the solid was diluted with MeOH and 30 concentrated *in vacuo*. The residue was diluted with EtOAc; washed with saturated NH₄Cl and H₂O, dried (MgSO₄) and concentrated *in vacuo* to afford the title compound as a

light-orange solid. MS m/z: 370.2 (M+H). Calc'd for C₁₈H₁₉N₅O₂S: 369.13.

Example 197

5



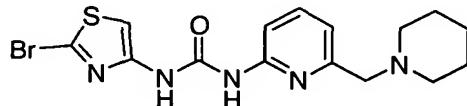
1-[2-(6-Methoxypyridin-3-yl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea

10

To a solution of the 3-(4-methoxy-3-pyridyl)thiazole carboxylic acid (200 mg, 0.85 mmol) and dry toluene (20 mL) was added (PhO)₂PON₃ (0.2 mL, 0.94 mmol) and TEA (0.13 mL, 0.94 mmol). The mixture was heated to 85°C for five min then 2-amino-6-methylpiperidinylpyridine (0.16 g, 0.85 mmol) in CH₃CN (3 mL) was added. The reaction was heated at reflux for 15 h then concentrated *in vacuo* and purified by silica flash chromatography (1% to 5% MeOH/CH₂Cl₂) to give the title compound as an orange oil. Diluted with MeOH (5 mL) and added one equivalent of 1M HCl in Et₂O. Concentrated *in vacuo* to afford the HCl salt as an orange solid. MS m/z: 424.9 (M+H). Calc'd for C₂₁H₂₄N₆O₂S: 424.17.

Example 198

25

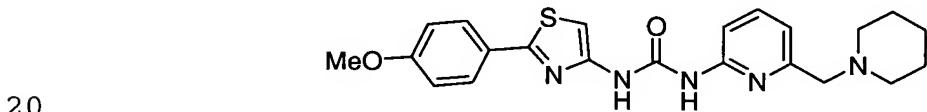


1-(2-Bromothiazol-4-yl)-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea

30

To a stirred suspension of 2-bromothiazole-4-carboxylic acid (5.13 g, 2 mmol) in anhydrous CH₃CN (40 ml) at RT, under N₂, TEA (3.80 ml, 27 mmol) and (PhO)₂PON₃ (5.90 ml, 27 mmol) were added. The resulting solution was heated 5 to 85°C. Upon reaching 85°C, a solution of 6-(piperidylmethyl)-2-pyridylamine (4.74 g, 25 mmol) in anhydrous CH₃CN (60 ml) was added. The reaction was maintained at this temperature for 2.25 h. After cooling to RT the mixture was diluted with CH₂Cl₂ (50 ml) then washed 10 with a saturated solution of NH₄Cl(aq) (40 ml). The organic layer was separated, dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (3:1/2:1/1:1, EtOAc:acetone) to yield the title compound as a pale yellow 15 solid. MS m/z: 396 (M+H), 398 (M+3). Calc'd for C₁₅H₁₈BrN₅OS: 395.04.

Example 199



1-[2-(4-Methoxyphenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea

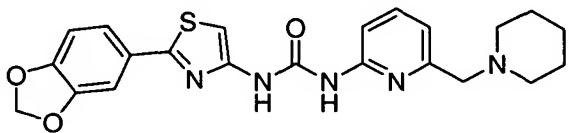
25 A stirred suspension of N-(2-bromo(1,3-thiazol-4-yl))([6-(piperidylmethyl)(2-pyridyl)]amino)carboxamide (2.23 g, 5.64 mmol), 4-methoxyphenylboronic acid (0.94 g, 6.21 mmol), PdCl₂(dppf)₂ (0.46 g, 0.56 mmol) and Na₂CO₃ (2.10 g, 17.0 mmol) in ethylene glycol dimethyl ether (25 ml) and H₂O 30 (8 ml) was heated at reflux for 12h. After cooling to RT the mixture was filtered through Celite®. The filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (3:1,

EtOAc:acetone) to yield the title compound as a pale yellow amorphous solid. MS m/z: 424 (M+H). Calc'd for C₂₂H₂₅N₅O₂S: 423.17.

5 The following compounds were prepared from the corresponding boronic acids in a manner similar to Example 199:

Example 200

10

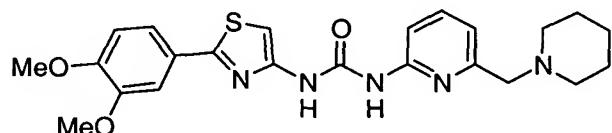


1-(2-Benzo[1,3]dioxol-5-yl-thiazol-4-yl)-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)-urea

15 MS m/z: 438 (M+H). Calc'd for C₂₂H₂₃N₅O₃S: 437.15.

Example 201

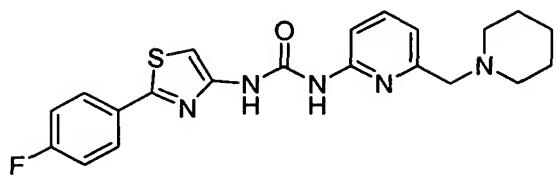
20



1-[2-(3,4-Dimethoxyphenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)-urea

MS m/z: 454 (M+H). Calc'd for C₂₃H₂₇N₅O₃S: 453.18.

25

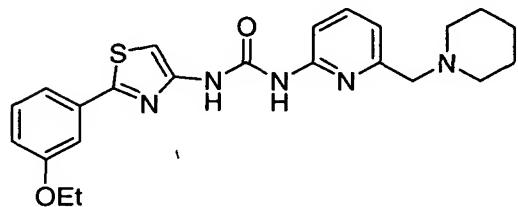
Example 202

5

1-[2-(4-Fluorophenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea

EI-MS m/z 412 (M+H). Calc'd for $C_{21}H_{22}FN_5OS$: 411.15.

10

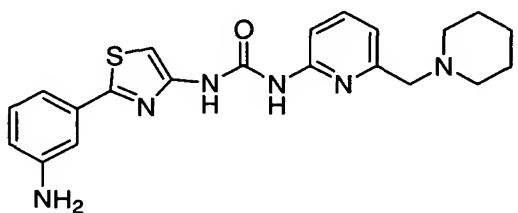
Example 203

15

1-[2-(3-Ethoxyphenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea

EI-MS m/z 438 (M+H). Calc'd for $C_{23}H_{27}N_5O_2S$: 437.19.

20

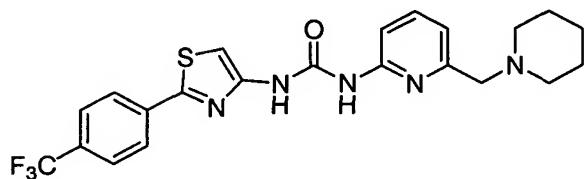
Example 204

1-[2-(3-Aminophenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea

EI-MS m/z 409 (M+H). Calc'd for C₂₁H₂₄N₆OS: 408.17.

5

Example 205

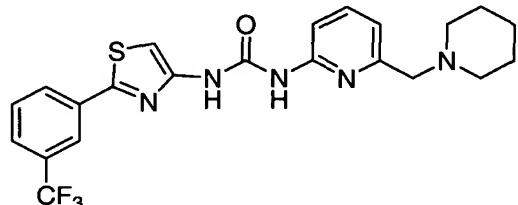


10 **1-[2-(4-Trifluoromethoxyphenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea**

EI-MS m/z 462 (M+H). Calc'd for C₂₂H₂₂F₃N₅OS: 461.15.

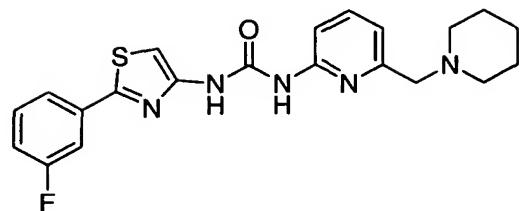
15

Example 206



20 **1-[2-(3-Trifluoromethoxyphenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea**

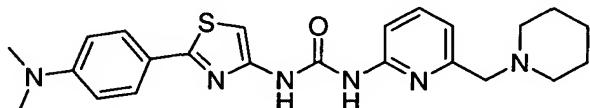
EI-MS m/z 462 (M+H)⁺. Calc'd for C₂₂H₂₂F₃N₅OS: 461.15.

Example 207

5

1-[2-(3-Fluorophenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea

10 EI-MS m/z 412 (M+H). Calc'd for C₂₁H₂₂FN₅OS: 411.15.

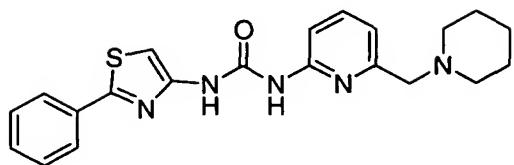
Example 208

15

1-[2-(4-Dimethylaminophenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea

20

EI-MS m/z 437 (M+H). Calc'd for C₂₃H₂₈N₆OS: 436.20.

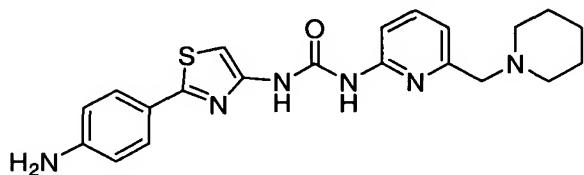
Example 209

5

1-[2-phenylthiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea

EI-MS m/z 394 (M+H). Calc'd for C₂₁H₂₃N₅OS: 393.16.

10

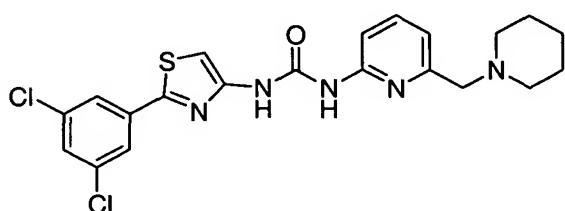
Example 210

15

1-[2-(4-Aminophenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea

EI-MS m/z 409 (M+H). Calc'd for C₂₁H₂₄N₆OS: 408.17.

20

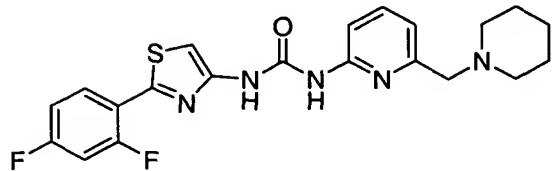
Example 211

1-[2-(3,5-Dichlorophenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea

EI-MS m/z 462 (M+H). Calc'd for C₂₁H₂₁Cl₂N₅OS: 461.08.

Example 212

5



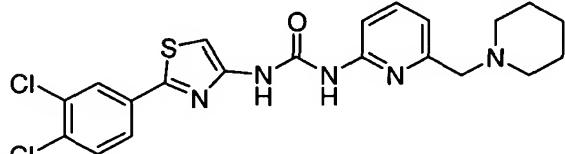
1-[2-(2,4-Difluorophenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea

10

EI-MS m/z 430 (M+H). Calc'd for C₂₁H₂₁F₂N₅OS: 429.14.

Example 213

15



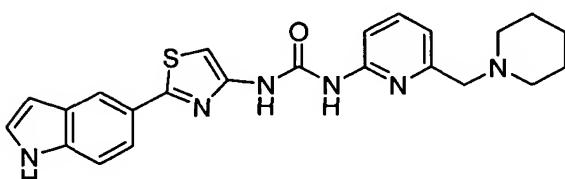
1-[2-(3,4-Dichlorophenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea

20

EI-MS m/z 462 (M+H). Calc'd for C₂₁H₂₁Cl₂N₅OS: 461.08.

Example 214

25



1-[2-(1H-Indol-5-yl)-thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)-urea

EI-MS m/z 433 (M+H). Calc'd for C₂₃H₂₄N₆OS: 432.17.

5

Example 215

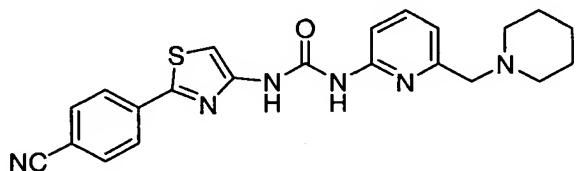


10 **1-[2-(4-Methylthiophenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea**

EI-MS m/z 440 (M+H). Calc'd for C₂₂H₂₅N₅OS₂: 439.15.

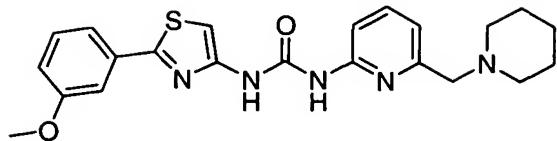
15

Example 216



20 **1-[2-(4-Cyanophenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea**

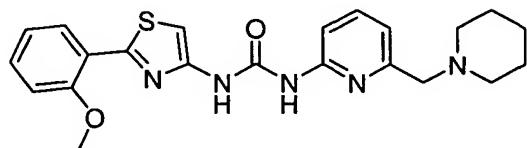
EI-MS m/z 419 (M+H). Calc'd for C₂₂H₂₂N₆OS: 418.16

Example 217

5 **1-[2-(3-Methoxyphenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea**

To a stirred solution of 2-(3-methoxyphenyl)-1,3-thiazole-4-carboxylic acid (0.17 g, 0.72 mmol) in toluene (10 mL) at RT and under N₂ was added TEA (0.2 mL). After 5 min, (PhO)₂PON₃ (0.25 mL) was added and the reaction mixture was heated at 85°C for 20 min followed by the addition of 6-(piperidylmethyl)-2-pyridylamine (0.21 g, 1.1 mmol). The resulting mixture was heated at reflux for 4 h using a Dean-Stark trap. The mixture was cooled to RT, concentrated by rotary evaporation and purified on silica gel (5:95 MeOH/CH₂Cl₂). The yellow solid obtained was dissolved in EtOAc (15mL) and washed with a saturated solution of NH₄Cl (aq). The organic phase was separated, dried over MgSO₄, filtered and concentrated by rotary evaporation. The product was recrystallized from hexanes to afford the title compound as a white solid. EI-MS m/z 424 (M+H). Calc'd for C₂₂H₂₅N₅O₂S: 423.17.

25

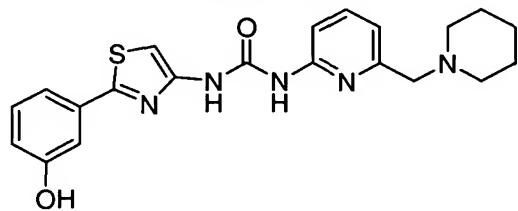
Example 218

1-[2-(2-Methoxyphenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea

To a stirred solution of 2-(2-methoxyphenyl)-1,3-thiazole-4-carboxylic acid (0.22 g, 0.94 mmol) in toluene (10 mL) at RT and under N₂ was added TEA (0.3 mL). After 5 min, (PhO)₂PON₃ (0.32 mL) was added and the reaction mixture was heated at 85°C for 20 min followed by the addition of 6-(piperidylmethyl)-2-pyridylamine (0.27 g, 1.41 mmol). The resulting mixture was heated at reflux for 4 h using a Dean-Stark trap. The mixture was cooled to RT, concentrated by rotary evaporation and purified on silica gel (5:95 MeOH/CH₂Cl₂). The yellow solid obtained was dissolved in EtOAc (15 mL) and washed with saturated NH₄Cl (10 mL). The organic phase was separated, dried over MgSO₄, filtered and concentrated by rotary evaporation to afford the title compound as a pale-yellow solid. EI-MS m/z 424 (M+H).
Calc'd for C₂₂H₂₅N₅O₂S: 423.17.

20

Example 219



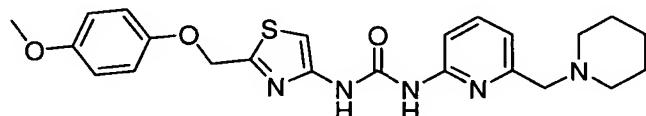
1-[2-(3-Hydroxyphenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea

25

A mixture of 1-[2-(3-methoxyphenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea (Example 218) and beryllium chloride (5.0 eq) in dry toluene (0.2 M) and 4A molecular sieves was heated at reflux for 10 h. The starting material was not totally soluble in toluene. The mixture was

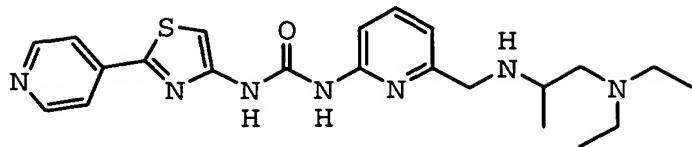
brought to RT, diluted with EtOAc and washed with saturated NH₄Cl. The organic phase was separated, dried over MgSO₄, filtered, concentrated by rotary evaporation and purified by prep HPLC (Column Phenomenex type Prodigy 50 ODS3 100A size 5 250x21.20mm 5u, Gradient 10% to 90% CH₃CN:H₂O containing 1% TFA over 20 min, Detector 254 nm, 4 nm Band) to afford the title compound as an off white solid. EI-MS m/z 410 (M+H). Calc'd for C₂₁H₂₃N₅O₂S: 409.16.

10

Example 220

15 **1-[2-(4-Methoxyphenoxy)methyl]thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea**

To a stirred solution of 2-[(4-methoxyphenoxy)-methyl]-1,3-thiazole-4-carboxylic acid (0.10 g, 0.38 mmol) and TEA (0.06 mL, 0.46 mmol) in dry toluene (15mL) and 4A° molecular sieves was added (PhO)₂PON₃ (0.10 mL, 0.46 mmol). The resulting mixture was heated at 85°C for 25 min followed by the addition of 6-(piperidyl-methyl)-2-pyridylamine (0.09 g, 0.46 mmol). The resulting mixture was heated to reflux for 15 h, cooled to RT, filtered, concentrated by rotary evaporation and purified on silica gel (5:95 MeOH/CH₂Cl₂) to afford the title compound as a yellow oil. EI-MS m/z 454 (M+H). Calc'd for C₂₃H₂₇N₅O₃S: 453.18.

Example 221

5 **1-{6-[(2-Diethylamino-1-methylethylamino)methyl]-pyridin-2-yl}-3-(2-pyridin-4-yl-thiazol-4-yl)urea**

Step A

To a stirred solution of N-[(6-amino(2-pyridyl)methyl)-N-[2-(diethylamino)-isopropyl](tert-butoxy)-carboxamide (30 mg, 0.09 mmol) in toluene (5 mL) was added 2-aza-2-diazo-1-(2-(4-pyridyl)(1,3-thiazol-4-yl)ethen-1-one (0.02 g, 0.09 mmol). The resulting green solution was heated to reflux in a Dean-Stark trap for 1.5 h until the starting materials were consumed. The mixture was brought to RT, concentrated by rotary evaporation and the residue obtained was partitioned between H₂O (10 mL) and CHCl₃ (10 mL). The organic phase was separated and the aqueous phase was extracted (3x10 mL) with CHCl₃. The organic layers were combined, dried over MgSO₄, filtered, concentrated by rotary evaporation and purified by prep TLC (10:90 MeOH/CH₂Cl₂) to afford *tert* butyl (2-dimethylamino-1-methyl-ethyl)-(6-[3-(2-pyridin-4-yl-thiazol-4-yl)ureido]pyridin-2-yl)carbamate as a white solid. EI-MS m/z 540 (M+H). Calc'd for C₂₇H₃₇N₇O₃S: 539.27.

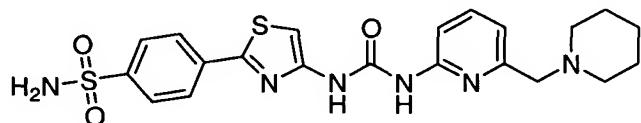
Step B

To a stirred solution of N-[2-diethylamino)-ethyl](tert-butoxy)-N-[(6-[(N-(2-(4-pyridyl)(1,3-thiazol-4-yl)carbamoyl)amino)(2-pyridyl)methyl]-carboxamide (4 mg, 0.007 mmol) in dry CH₂Cl₂ (1 mL) was added TFA (1 mL). The resulting solution was stirred at RT and under N₂ atmosphere

for 2 h, concentrated by rotary evaporation and the residue was diluted with EtOAc (5 mL) and washed with a saturated solution of NaHCO₃ (aq) (15 mL). The organic phase was separated, dried over MgSO₄, filtered, concentrated by 5 rotary evaporation and purified by prep TLC (1:1 MeOH/CH₂Cl₂) to yield 1-{6-[(2-diethylamino-1-methylethylamino)methyl]-pyridin-2-yl}-3-(2-pyridin-4-yl-thiazol-4-yl)urea. EI-MS m/z 540 (M+H). Calc'd for C₂₂H₂₉N₇OS: 439.22.

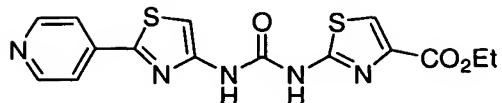
10

Example 222



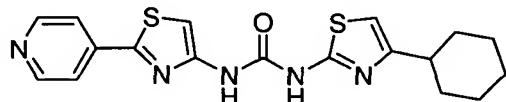
15 **4-{4-[(3-(6-Piperidin-1-ylmethyl-pyridin-2-yl)-ureido)-thiazol-2-yl]-benzenesulfonamide}**

To a stirred solution of ethyl 2-(4-sulfamoyl-phenyl)-1,3-thiazole-4-carboxylic acid (90 mg, 0.32 mmol) in dry TFA 20 (3 mL) and 4A molecular sieves at RT and under N₂ was added TEA (0.1 mL). After 5 min, (PhO)₂PON₃ (0.11 mL) and 6-(piperidylmethyl)-2-pyridylamine (0.10 g, 0.51 mmol) were added and the reaction mixture was heated to reflux for 4 h and then cooled to RT. The mixture was washed with 10% HCl 25 (aq) and extracted with EtOAc (3x10 mL). The aqueous layer was brought to a pH 8.0 and extracted with CH₂Cl₂ (3x20mL). The extracts were combined, dried over MgSO₄, concentrated by rotary evaporation and purified on silica gel (2:1 hexanes/EtOAc and 1:1 MeOH/CH₂Cl₂) to afford the title 30 compound as a pale yellow solid. EI-MS m/z 473 (M+H). Calc'd for C₂₁H₂₄N₆O₃S₂: 472.14.

Example 223

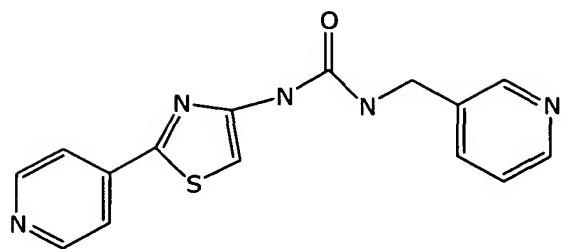
5 **Ethyl 2-[3-[2-(pyridin-4-yl)-thiazol-4-yl]ureido]-thiazole-4-carboxylate**

2- (4-Pyridinyl)-4-thiazolcarbonylazide (420 mg, 1.8 mmol) in dry toluene (20 mL) was heated to 85°C under N₂ and 10 maintained at this temperature for 5 min. A solution of 2-amino-4-thiazolcarboxylic acid ethyl ester (350 mg, 2.0 mmol) was added and the resulting mixture was heated at 85°C for 15 h. After cooling to RT, a precipitate formed and was filtered to give the desired compound as a yellow solid. MS 15 m/z: 376.0 (M+H). Calc'd for C₁₅H₁₃N₅O₃S₂: 375.05.

Example 224

20 **1-(4-Cyclohexylthiazol-2-yl)-3-[(2-(pyridin-4-yl)-4-thiazolcarbonylazide)ureido]thiazole-4-carboxylate**

2- (4-Pyridinyl)-4-thiazolcarbonylazide (200 mg, 0.87 mmol) in dry toluene (10 mL) was heated to 85°C under N₂ and 25 maintained at this temperature for 5 min. A solution of 2-amino-4-cyclohexylthiazole (158 mg, 0.87 mmol) was added and the resulting mixture was heated at 85°C for 15 h. After 30 cooling to RT, a precipitate formed and was filtered to give the desired compound as a yellow solid. MS m/z: 386.0 (M+H). Calc'd for C₁₈H₁₉N₅OS₂: 385.10.

Example 225

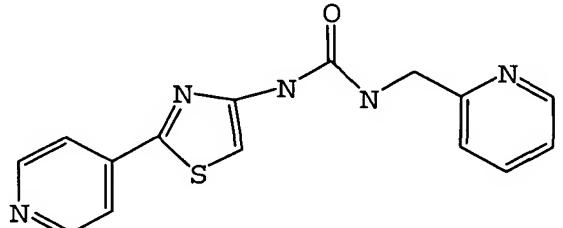
5

1-(Pyridin-3-ylmethyl)-3-(2-pyridin-4-yl-thiazol-4-yl)urea

2-(4-Pyridinyl)-4-thiazolcarbonylazide (100 mg, 0.43 mmol) in dry toluene (3 mL) was heated to 105°C under N₂ and 10 maintained at this temperature for 5 min. A solution of 3-(aminomethyl)pyridine (47 mg, 0.43 mmol) in dry toluene (1 mL) was added dropwise via syringe and the resulting mixture heated at 105°C for 2 h. After cooling to RT, solvent was removed under vacuum and the product was purified by silica 15 gel chromatography eluting with MeOH/CH₂Cl₂ (10%) to give the desired compound as a light yellow solid. MS m/z: 312.1 (M+H). Calc'd for C₁₅H₁₃N₅OS: 311.08.

Example 226

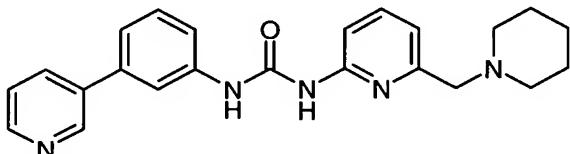
20

**1-(Pyridin-2-ylmethyl)-3-(2-pyridin-4-yl-thiazol-4-yl)urea**

2-(4-Pyridinyl)-4-thiazolcarbonylazide (100 mg, 0.43 mmol) in dry toluene (3 mL) was heated to 105°C under N₂ and maintained at this temperature for 5 min. A solution of 2-(aminomethyl)pyridine (47 mg, 0.43 mmol) in dry toluene (1 mL) was then added dropwise via syringe and the resulting mixture heated at 105°C for 3 h. After cooling to RT, solvent was removed under vacuum and the product was purified by silica gel chromatography eluting with MeOH/CH₂Cl₂ (10%) to give a light yellow solid. MS m/z: 312.1 (M+H). Calc'd for C₁₅H₁₃N₅OS: 311.08.

Example 227

15



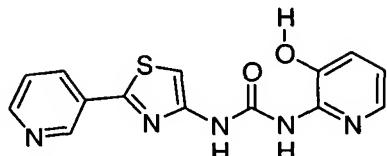
1-[6-(Piperidin-1-ylmethyl)pyridin-2-yl]-3-(3-pyridin-3-ylphenyl)urea

20 To a stirred solution of phosgene (0.35 mL, 0.65 mmol, 20% in toluene) in dry THF (5 mL) was added 3-(3-pyridin-1-yl)-1-aminobenzene (85 mg, 0.5 mmol) dropwise via the addition funnel. After stirring for 10 min, isopropylethylamine (0.26 mL, 2.0 mmol) was added. The 25 resulting mixture was stirred at RT under N₂ for 30 min. 2-Amino-6-piperidinylmethylpyridine (96 mg, 0.5 mmol) in dry THF (5 mL) was added dropwise into the reaction mixture via the addition funnel. The resulting mixture was stirred at RT for 15 h. Solvent was removed to give a dark brown 30 liquid which was purified by chromatography on silica gel. Elution with CH₂Cl₂:MeOH mixture (95:5) gave the final

compound as a pale yellow solid. MS m/z : 387.9 (M $^+$).
Calc'd. for C₂₃H₂₅N₅O - 387.49.

Example 228

5

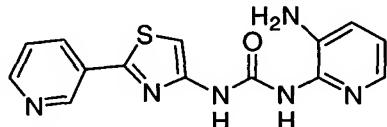


1-(3-Hydroxy-pyridin-2-yl)-3-(2-pyridin-3-yl-thiazol-4-yl)-urea

10 TEA (0.27 mL, 1.94 mmol) was added to a solution of 2-(pyridin-3-yl)thiazole-4-carboxylic acid (200 mg, 0.97 mmol) and 4A molecular sieves in THF (25 mL) under N₂ at RT. (PhO)₂PON₃ (0.33 mL, 1.55 mmol) followed by 2-amino-6-hydroxypyridine (268 mg, 2.43 mmol) was added and the
15 resulting mixture heated at reflux for 12 h. After cooling to RT, the heterogeneous mixture was decanted to remove the molecular sieves. The precipitate was collected, rinsing with EtOAc to give a white solid. MS m/z : 313.0 (M+H).
Calc'd for C₁₄H₁₁N₅O₂S - 313.34.

20

Example 229

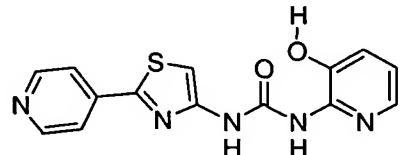


25 **1-(3-Amino-pyridin-2-yl)-3-(2-pyridin-3-yl-thiazol-4-yl)-urea**

TEA (0.27 mL, 1.94 mmol) was added to a solution of 2-(pyridin-3-yl)thiazole-4-carboxylic acid (200 mg, 0.97 mmol)

and 4A molecular sieves in THF (25 mL) under N₂ at RT. (PhO)₂PON₃ (0.33 mL, 1.55 mmol) followed by 2-amino-3-aminomethylpyridine (265 mg, 2.43 mmol) was added and the resulting mixture was heated at reflux for 12 h. After 5 cooling to RT, the heterogeneous mixture was decanted to remove the molecular sieves. The precipitate was collected and discarded. The filtrate was purified by chromatography on silica gel (CH₂Cl₂/MeOH, 95:5) to give a white solid. MS *m/z*: 313.8 (M+H). Calc'd for C₁₄H₁₂N₆OS - 312.36.

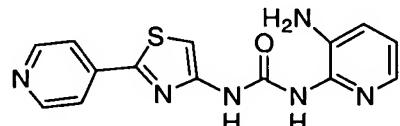
10

Example 230

15 **1-(3-Hydroxy-pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)-urea**

20 2-(4-Pyridinyl)-4-thiazolcarbonylazide (200 mg, 0.86 mmol) and 2-amino-3-hydroxymethylpyridine (95 mg, 0.86 mmol) in dry toluene (10 mL) were heated at 100°C for 12 h to give a pale yellow solid which was recrystallized from CHCl₃/MeOH (99:5) to give a pale yellow solid. MS *m/z*: 314.0 (M+H). Calc'd for C₁₄H₁₁N₅O₂S - 313.34.

25

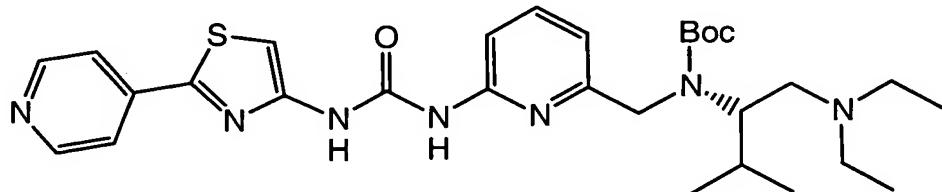
Example 231

1-(3-Amino-pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

5 2-(4-Pyridinyl)-4-thiazolcarbonylazide (200 mg, 0.86 mmol) and 2-amino-3-aminomethylpyridine (94 mg, 0.86 mmol) in dry toluene (10 mL) were heated at 100°C for 12 h to give a pale yellow solid which was recrystallized from CHCl₃/MeOH (99:5) to give a pale yellow solid. MS *m/z*: 313.0 (M+H). Calc'd for C₁₄H₁₂N₆OS - 312.36.

10

Example 232

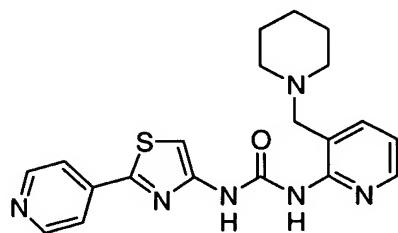


15 **(1-Diethylaminomethyl-2-methyl-propyl)-{6-[3-(2-pyridin-4-yl-thiazol-4-yl)-ureido]-pyridin-2-ylmethyl}-carbamic acid tert-butyl ester**

To a stirred solution of N-[(6-amino-(2-pyridyl))-methyl]-N-{1-[(diethylamino)methyl]-2-methylpropyl}-(*tert*-butoxy)carboxamide (6 mg, 0.016 mmol) in toluene (5 mL) was added 6-(piperidylmethyl)-2-pyridylamine (0.004 g, 0.016 mmol). The resulting green solution was heated at reflux in a Dean-Stark trap for 1.5 h until the starting materials were consumed. The mixture was brought to RT, concentrated by rotary evaporation and the residue obtained was partitioned between H₂O (10 mL) and CHCl₃ (35 mL). The organic phase was separated and the aqueous phase was extracted with CHCl₃ (3x10mL). The organic layers were combined, dried over MgSO₄, filtered, concentrated by rotary evaporation and purified by prep TLC (5:95 MeOH/CH₂Cl₂) to afford (1-diethylaminomethyl-2-methyl-propyl)-{6-[3-(2-

pyridin-4-yl-thiazol-4-yl)-ureido]-pyridin-2-ylmethyl}-carbamic acid *tert*-butyl ester as an off-white solid. EI-MS m/z 568 (M+H). Calc'd for C₂₉H₄₁N₇O₃S: 567.30.

5

Example 233

10 1-(3-Piperidin-1-ylmethyl-pyridin-2-yl)-3-(2-pyridin-4-yl-

thiazol-4-yl)-urea

MS m/z: 395 (M+H). Calc'd MS C₂₀H₂₂N₆OS - 394.49.

Example 234

15

16 1-(2-Pyridin-4-yl-thiazol-4-yl)-3-[6-(2,2,6,6-tetramethyl-piperidin-1-ylmethyl)-pyridin-2-yl]-urea

20

2-(4-Pyridinyl)-4-thiazolcarbonylazide (35 mg, 0.15

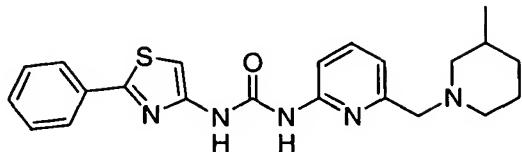
mmol) in dry toluene (10 mL) was heated to 80°C under N₂ and maintained at this temperature for 10 min. A solution of 6-(2,2,6,6-tetramethyl-piperidin-1-ylmethyl)-pyridin-2-ylamine

25 (30 mg, 0.12 mmol) in dry toluene (2 mL) was added dropwise via syringe and the resulting mixture heated at 85°C for 3 h. After cooling to RT, the crude mixture was purified by chromatography on silica gel (MeOH/CHCl₃, 3:97) to give a

pale yellow solid. MS *m/z*: 449.3 (M-H). Calc'd for C₂₄H₃₀N₆OS - 450.60.

Example 235

5

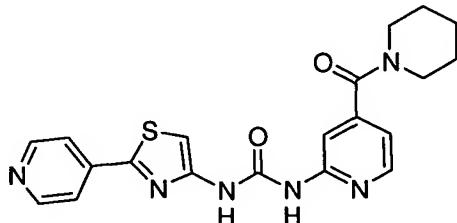


1-[6-(3-Methyl-piperidin-1-ylmethyl)-pyridin-2-yl]-3-(2-phenyl-thiazol-4-yl)-urea

10

In a manner similar to that described in Example 234, 2-(4-pyridinyl)-4-thiazolcarbonylazide (100 mg, 0.43 mmol) in dry toluene (10 mL) was heated with 6-(3-methyl-piperidin-1-ylmethyl)-pyridin-2-ylamine (106 mg, 0.52 mmol) to give an off-white solid. MS *m/z*: 408.3 (M+H). Calc'd for C₂₂H₂₅N₅OS - 407.53.

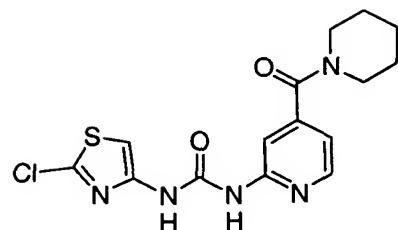
Example 236



20

1-[4-(Piperidine-1-carbonyl)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

In a manner similar to that described in Example 234, 2-(4-pyridinyl)-4-thiazolcarbonylazide (100 mg, 0.43 mmol) was heated with (2-amino-pyridin-4-yl)-piperidin-1-yl-methanone (88 mg, 0.43 mmol) in dry toluene (10 mL) to give a white solid. MS *m/z*: 409.3 (M+H). Calc'd. for C₂₀H₂₀N₆O₂S - 408.14.

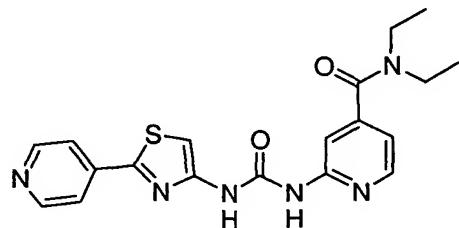
Example 237

5

1-(2-Chloro-thiazol-4-yl)-3-[4-(piperidine-1-carbonyl)-pyridin-2-yl]-urea

In a manner similar to that described in Example 234,
 10 2-chloro-4-thiazolcarbonylazide (74 mg, 0.39 mmol) was
 heated with 4-piperidin-1-ylmethyl-pyridin-2-ylamine (80 mg,
 0.39 mmol) in dry toluene (10 mL) to give a white solid. MS
 m/z: 366.2 (M+H). Calc'd. for $C_{15}H_{16}ClN_5O_2S$ - 365.07.

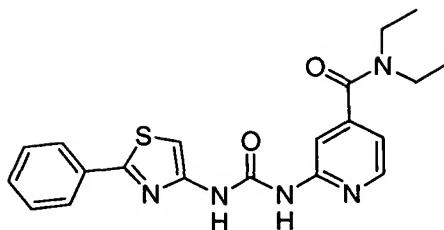
15

Example 238

20

N,N-Diethyl-2-[3-(2-pyridin-4-yl-thiazol-4-yl)-ureido]-isonicotinamide

In a manner similar to that described in Example 234,
 2-(4-pyridinyl)-4-thiazolcarbonylazide (95 mg, 0.41 mmol)
 was heated with 2-amino-N,N-diethyl-isonicotinamide (80 mg,
 0.41 mmol) in dry toluene (10 mL) to give a white solid. MS
 m/z: 397.2 (M+H). Calc'd. for $C_{19}H_{20}N_6O_2S$ - 396.14.

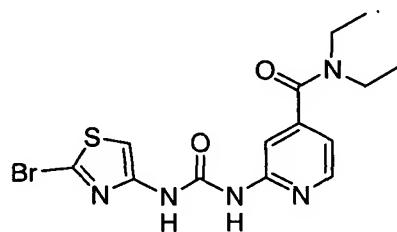
Example 239

5

N,N-Diethyl-2-[3-(2-phenyl-thiazol-4-yl)-ureido]-isonicotinamide

In a manner similar to that described in Example 234,
 10 2-phenyl-4-thiazolcarbonylazide (83 mg, 0.36 mmol) was
 heated with 2-amino-N,N-diethyl-isonicotinamide (70 mg, 0.36
 mmol) in dry toluene (10 mL) to give a white solid. MS m/z:
 396.3 (M+H). Calc'd. for C₁₉H₂₀N₆O₂S - 395.14.

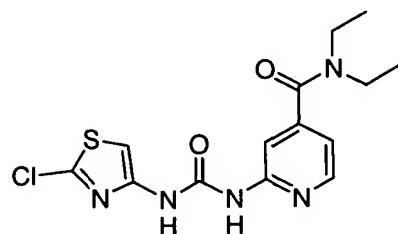
15

Example 240

20

2-[3-(2-Bromo-thiazol-4-yl)-ureido]-N,N-diethyl-isonicotinamide

In a manner similar to that described in Example 234,
 2-bromo-4-thiazolcarbonylazide (85 mg, 0.36 mmol) was heated
 with 2-amino-N,N-diethyl-isonicotinamide (70 mg, 0.36 mmol)
 25 in dry toluene (10 mL) to give a white solid. MS m/z: 398.1
 (M+H). Calc'd. for C₁₄H₁₆BrN₅O₂S - 397.02.

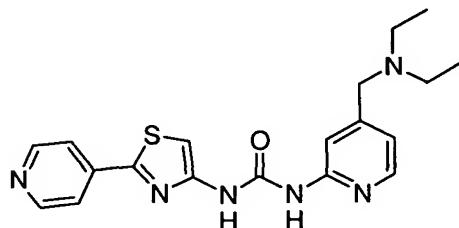
Example 241

5

**2-[3-(2-Chloro-thiazol-4-yl)-ureido]-N,N-diethyl-
isonicotinamide**

In a manner similar to that described in Example 234,
10 2-chloro-4-thiazolcarbonylazide (50 mg, 0.26 mmol) was
heated with 2-amino-N,N-diethyl-isonicotinamide (50 mg, 0.26
mmol) in dry toluene (10 mL) to give a white solid. MS m/z:
354.2 (M+H). Calc'd. for $C_{14}H_{16}ClN_5O_2S$ - 353.07.

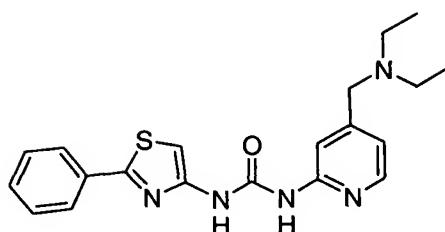
15

Example 242

20

**1-(4-Diethylaminomethyl-pyridin-2-yl)-3-(2-pyridin-4-yl-
thiazol-4-yl)-urea**

In a manner similar to that described in Example 234,
2-(4-pyridinyl)-4-thiazolcarbonylazide (78 mg, 0.34 mmol)
was heated with 4-diethylaminomethyl-pyridin-2-ylamine (60
25 mg, 0.34 mmol) in dry toluene (10 mL) to give a white solid.
MS m/z: 383.2 (M+H). Calc'd. for $C_{19}H_{22}N_6OS$ - 382.16.

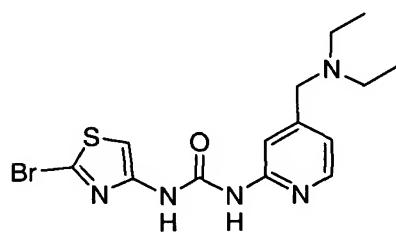
Example 243

5

1-(4-Diethylaminomethyl-pyridin-2-yl)-3-(2-phenyl-thiazol-4-yl)-urea

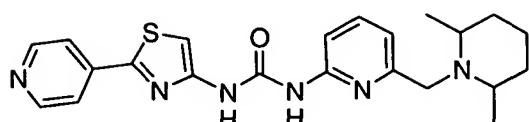
In a manner similar to that described in Example 234,
10 2-phenyl-4-thiazolcarbonylazide (77 mg, 0.34 mmol) was
heated with 4-diethylaminomethyl-pyridin-2-ylamine (60 mg,
0.34 mmol) in dry toluene (10 mL) to give a white solid. MS
m/z: 382.1 (M+H). Calc'd. for $C_{19}H_{22}N_6OS$ - 381.16.

15

Example 244

1-(2-Bromo-thiazol-4-yl)-3-(4-diethylaminomethyl-pyridin-2-yl)-urea

In a manner similar to that described in Example 234,
20 2-bromo-4-thiazolcarbonylazide (85 mg, 0.36 mmol) was heated
with 4-diethylaminomethyl-pyridin-2-ylamine (65 mg, 0.36
mmol) in dry toluene (10 mL) to give a white solid. MS m/z:
384.1 (M+H). Calc'd. for $C_{14}H_{18}BrN_5OS$ - 383.04.

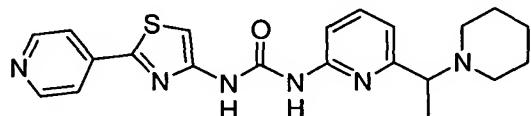
Example 245

5

1-[6-(2,6-Dimethyl-piperidin-1-ylmethyl)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

In a manner similar to that described in Example 234,
 10 2-(4-pyridinyl)-4-thiazolcarbonylazide (132 mg, 0.57 mmol)
 was heated with 6-(2,6-dimethyl-piperidin-1-ylmethyl)-
 pyridin-2-ylamine (125 mg, 0.57 mmol) in dry toluene (10 mL)
 to give a yellow solid. MS m/z: 423.3 (M+H). Calc'd. for
 $C_{22}H_{26}N_6OS$ - 422.19.

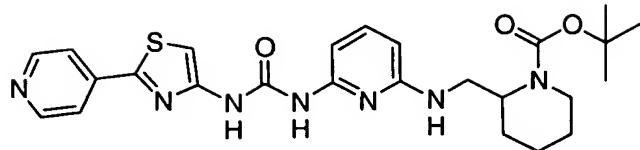
15

Example 247

20 **1-[6-(1-Piperidin-1-yl-ethyl)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea**

In a manner similar to that described in Example 234,
 25 2-(4-pyridinyl)-4-thiazolcarbonylazide (180 mg, 0.78 mmol)
 was heated with 6-(1-piperidin-1-yl-ethyl)-pyridin-2-ylamine
 (160 mg, 0.78 mmol) in dry toluene (10 mL) to give a yellow
 solid. MS m/z: 409.2 (M+H). Calc'd. for $C_{21}H_{24}N_6OS$ -
 408.17.

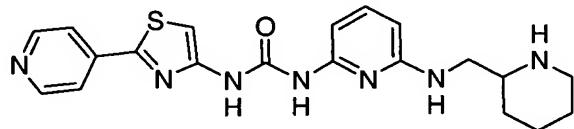
30

Example 248

5 **2-((6-(3-(2-pyridin-4-yl-thiazol-4-yl)-ureido)-pyridin-2-ylamino)-methyl)-piperidine-1-carboxylic acid tert-butyl ester**

In a manner similar to that described in Example 234,
10 2-(4-pyridinyl)-4-thiazolcarbonylazide (45 mg, 0.196 mmol)
 was heated with 2-[(6-amino-pyridin-2-ylamino)-methyl]-
 piperidine-1-carboxylic acid *tert*-butyl ester (60 mg, 0.196
 mmol) in dry toluene (10 mL) to give a yellow solid. MS
 m/z: 510.4 (M+H). Calc'd. for C₂₅H₃₁N₇O₃S - 509.2.

15

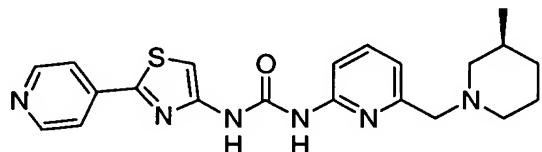
Example 249

20 **1-((6-((piperidin-2-ylmethyl)amino)-pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)-urea**

25 **2-((6-(3-(2-pyridin-4-yl-thiazol-4-yl)-ureido)-pyridin-2-ylamino)-methyl)-piperidine-1-carboxylic acid *tert*-butyl ester** (52 mg, 0.102 mmol) in MeOH (10 mL) was treated with TFA (0.1 mL, 1.3 mmol). The resulting mixture was heated at 50°C for 24 h. The reaction mixture was cooled to RT and neutralized to pH between 8-9. Solvent was removed. The residue was partitioned between H₂O and CHCl₃.

The organic layer was washed with H_2O , brine, dried over $MgSO_4$, and concentrated to give a yellow solid. MS m/z: 410.2 (M+H). Calc'd. for $C_{20}H_{23}N_7OS$ - 409.17.

5

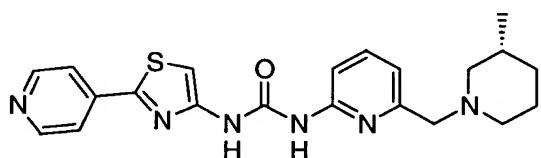
Example 250

(S)-1-[6-(3-Methyl-piperidin-1-ylmethyl)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

10

1-[6-(3-Methyl-piperidin-1-ylmethyl)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea (50 mg, 0.12 mmol, Example 78) was separated by chiral HPLC (Chiraltech Chiralcel OJ 50 x 4.6 mm i.d.) using hexane/EtOH/DEA (90:10:0.2) to give a white solid. MS m/z: 409.3 (M+H). Calc'd for $C_{21}H_{24}N_6OS$ - 408.52.

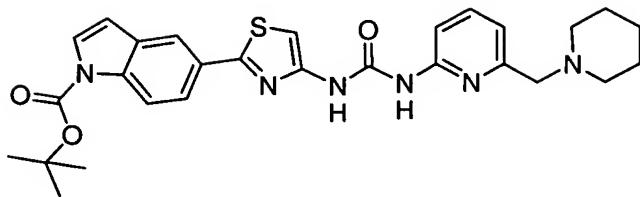
20

Example 251

(R)-1-[6-(3-Methyl-piperidin-1-ylmethyl)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

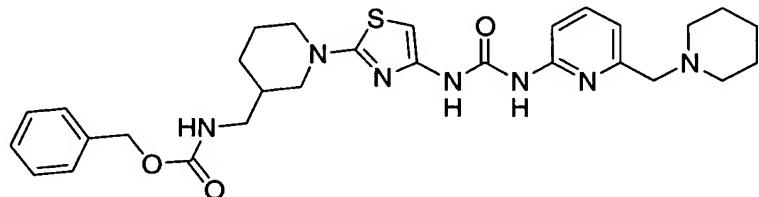
25

1-[6-(3-Methyl-piperidin-1-ylmethyl)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea (50 mg, 0.12 mmol, Example 78) was separated by chiral HPLC (Chiraltech Chiralcel OJ 50 x 4.6 mm i.d.) using hexane/EtOH/DEA (90:10:0.2) to give a white solid. MS m/z: 409.3 (M+H). Calc'd for $C_{21}H_{24}N_6OS$ - 408.52.

Example 252

5 **5-{4-[3-(6-Piperidin-1-ylmethyl)pyridin-2-yl]-ureido}thiazol-2-yl)-indole-1-carboxylic acid *tert*-butyl ester**

To a solution of 5-(4-carboxy-thiazol-2-yl)-indole-1-carboxylic acid *tert*-butyl ester (2.65 g, 7.69 mmol),
 10 molecular sieves, and 100 mL of dry toluene was added TEA (1.6 mL, 11.5 mmol). The resulting solution was stirred for 20 min then DPPA (2.5 mL, 11.6 mmol) was added and the resulting solution was stirred at 80°C for 40 min. 6-Piperidin-1-ylmethyl-pyridin-2-ylamine (1.64 g, 8.6 mmol) and
 15 pyridine (1.0 mL, 12.4 mmol) were added and the mixture was stirred at 80°C for another 14 h. The molecular sieves were filtered off and washed with CH₂Cl₂ and MeOH. The filtrate was concentrated *in vacuo* and the resulting residue was purified by flash chromatography on silica gel using 3% MeOH/CH₂Cl₂ to give a brown solid. MS *m/z*: 533 (M+1).
 20 Calc'd for C₂₈H₃₂N₆O₃S - 532.66.

Example 253

(1-{4-[3-(6-Piperidin-1-ylmethyl-pyridin-2-yl)-ureido]-thiazol-2-yl}-piperidin-3-ylm thyl)-carbamic acid benzyl ester

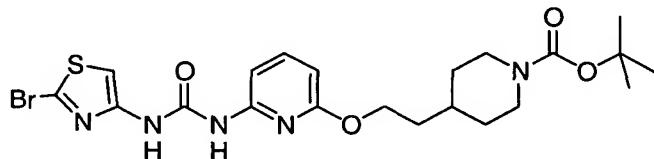
5 To a stirred solution of 2-[3-(benzyloxy-carbonylamino-methyl)-piperidin-1-yl]-thiazole-4-carboxylic acid (351 mg, 0.93 mmol) in anhydrous toluene (15 mL), under N₂, at RT, over 4A activated molecular sieves, TEA (0.16 mL, 1.12 mmol) was added. After 7 min, DPPA (0.24 mL, 1.12 mmol) was added and the solution was heated to 85°C for 20 min. Neat 6-piperidin-1-ylmethyl-pyridin-2-ylamine (179 mg, 0.93 mmol) was added and the reaction was maintained at 85°C for an additional 2.5 h. After cooling to RT the solution was filtered through a Celite® pad that was washed

10 successively with CH₂Cl₂ (4 x 5 mL). The filtrate was evaporated *in vacuo* and the residue purified by flash chromatography on silica gel (97:3, CHCl₃:MeOH) to yield the title compound as a red/orange oil. MS *m/z*: 564.4 (M+H).
Calc'd. for C₂₉H₃₇N₇O₃S - 563.72.

15

20

Example 254



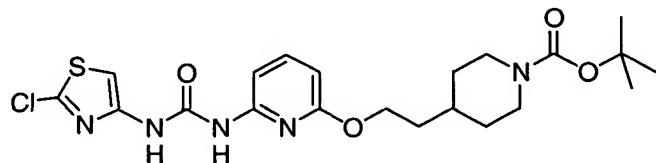
25 **4-(2-{6-[3-(2-Bromo-thiazol-4-yl)-ureido]-pyridin-2-yloxy}-ethyl)-piperidine-1-carboxylic acid *tert*-butyl ester**

30 To a stirred solution of 2-bromo-thiazole-4-carbonyl azide (194 mg, 0.83 mmol) in anhydrous toluene (4 mL) under N₂, that had been heated to 85°C and held there for 5 min, a solution of 4-[2-(6-amino-pyridin-2-yloxy)-ethyl]-

piperidine-1-carboxylic acid *tert*-butyl ester (268 mg, 0.83 mmol) in anhydrous toluene (3 mL) was added over 5 min. After 3 h the reaction mixture was cooled to RT. The precipitate was filtered off to yield the title compound as 5 a white amorphous solid. MS *m/z*: 526.1, 528.1 (M+H). Calc'd. for $C_{21}H_{28}BrN_5O_4S$ - 526.4.

The following Examples 255 - 263 were prepared from their 10 respective amines and azides in a manner similar to example 254.

Example 255

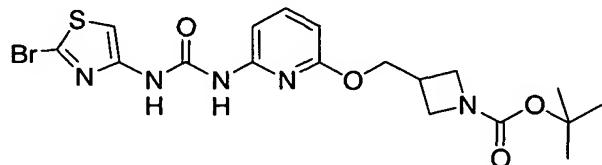


15

4-(2-{6-[3-(2-Chloro-thiazol-4-yl)-ureido]-pyridin-2-yloxy}-ethyl)-piperidine-1-carboxylic acid *tert*-butyl ester

20 MS *m/z*: 482.3 (M+H). Calc'd. for $C_{21}H_{28}ClN_5O_4S$ - 482.00.

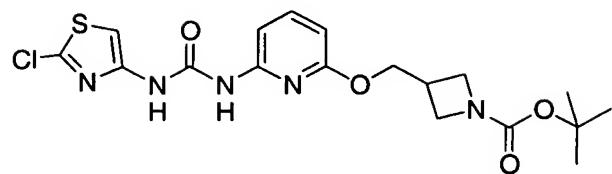
Example 256



25

3-{6-[3-(2-Bromo-thiazol-4-yl)-ureido]-pyridin-2-yloxy-methyl}-azetidine-1-carboxylic acid *tert*-butyl ester

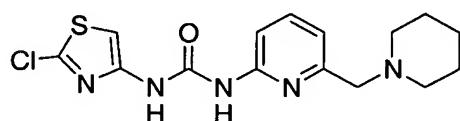
30 MS *m/z*: 484.1, 486.1 (M+H). Calc'd. for $C_{18}H_{22}BrN_5O_4S$ - 484.37.

Example 257

5 3-{6-[3-(2-Chloro-thiazol-4-yl)-ureido]-pyridin-2-yloxyethyl}-azetidine-1-carboxylic acid tert-butyl ester

MS *m/z*: 440.1 (M+H). Calc'd. for C₁₈H₂₂ClN₅O₄S - 439.92.

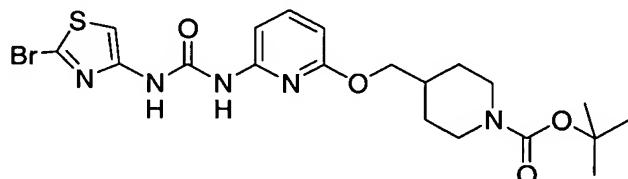
10

Example 258

15 1-(2-Chloro-thiazol-4-yl)-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)-urea

MS *m/z*: 352.3 (M+H). Calc'd. for C₁₅H₁₈ClN₅OS - 351.86.

20

Example 259

25 4-{6-[3-(2-Bromo-thiazol-4-yl)-ureido]-pyridin-2-yloxyethyl}-piperidine-1-carboxylic acid tert-butyl ester

MS *m/z*: 512.3, 514.3 (M+H). Calc'd. for $C_{20}H_{26}BrN_5O_4S$ - 512.42.

Example 260

5



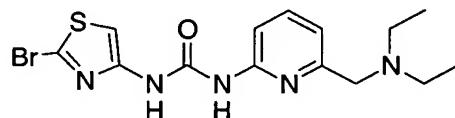
4-{6-[3-(2-Chloro-thiazol-4-yl)-ureido]-pyridin-2-yloxyethyl}-piperidine-1-carboxylic acid tert-butyl ester

10

MS *m/z*: 468.1 (M+H). Calc'd. for $C_{20}H_{26}ClN_5O_4S$ - 467.97.

Example 261

15



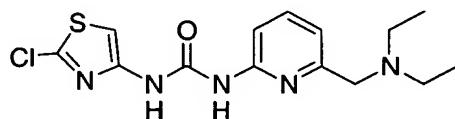
1-(2-Bromo-thiazol-4-yl)-3-(6-diethylaminomethyl-pyridin-2-yl)-urea

20

MS *m/z*: 384.1, 386.1 (M+H). Calc'd. for $C_{14}H_{18}BrN_5OS$ - 384.30.

Example 262

25

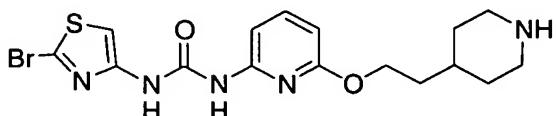


1-(2-Chloro-thiazol-4-yl)-3-(6-diethylaminomethyl-pyridin-2-yl)-urea

MS *m/z*: 340.2 (M+H). Calc'd. for C₁₄H₁₈ClN₅OS - 339.84.

5

Example 263



10 **1-(2-Bromo-thiazol-4-yl)-3-[6-(2-piperidin-4-yl-ethoxy)-pyridin-2-yl]-urea**

To a stirred solution of 4-(2-[6-[3-(2-bromo-thiazol-4-yl)-ureido]-pyridin-2-yloxy]-ethyl)-piperidine-1-carboxylic acid *tert*-butyl ester (285 mg, 0.54 mmol) in anhydrous CH₂Cl₂ (6 mL) at RT, under N₂, TFA (1.5 mL) was added. After 1.5 h the solvent was evaporated *in vacuo*. The residue was carefully treated with a saturated solution of NaHCO₃ (aq) (10 mL), the precipitate was filtered off, washed with Et₂O (3 x 5mL) and dried in a vacuum oven at 60°C for 5 h to yield the title compound as a white amorphous solid. MS *m/z*: 426.2, 428.2 (M+H). Calc'd. for C₁₆H₂₀BrN₅O₂S - 426.33.

15

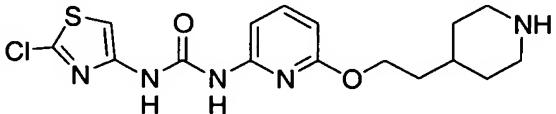
20

25

The following Examples 264 - 268 were prepared from their respective *tert*-butyl esters in a manner similar to example 263.

Example 264

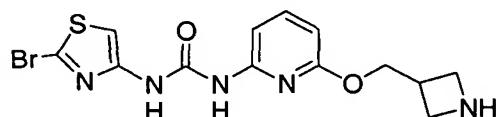
30



1-(2-Chloro-thiazol-4-yl)-3-[6-(2-pyridin-4-yl-ethoxy)-pyridin-2-yl]-urea

5 MS *m/z*: 382.3 (M+H). Calc'd. for C₁₆H₂₀ClN₅O₂S - 381.88.

Example 265

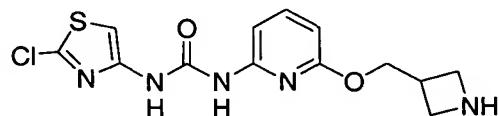


10

1-[6-(Azetidin-3-ylmethoxy)-pyridin-2-yl]-3-(2-bromo-thiazol-4-yl)-urea

15 MS *m/z*: 384.0, 386.0 (M+H). Calc'd. for C₁₃H₁₄BrN₅O₂S - 384.25.

Example 266

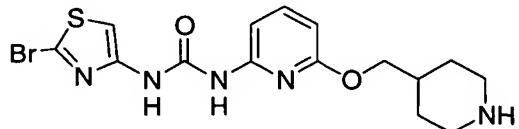


20

1-[6-(Azetidin-3-ylmethoxy)-pyridin-2-yl]-3-(2-chloro-thiazol-4-yl)-urea

25 MS *m/z*: 340.1 (M+H). Calc'd. for C₁₃H₁₄ClN₅O₂S - 339.80.

Example 267

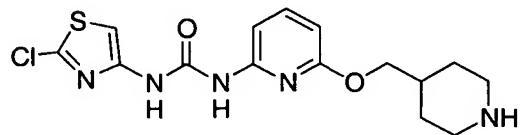


1-(2-Bromo-thiazol-4-yl)-3-[6-(piperidin-4-ylmethoxy)-pyridin-2-yl]-urea

5 MS *m/z*: 412.0, 414.0 (M+H). Calc'd. for C₁₅H₁₈BrN₅O₂S - 412.31.

Example 268

10

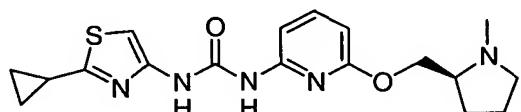


1-(2-Chloro-thiazol-4-yl)-3-[6-(piperidin-4-ylmethoxy)-pyridin-2-yl]-urea

15 MS *m/z*: 368.2 (M+H). Calc'd. for C₁₅H₁₈ClN₅O₂S - 367.85.

Example 269

20



1-(2-Cyclopropyl-thiazol-4-yl)-3-[6-(1-methyl-pyrrolidin-2-ylmethoxy)-pyridin-2-yl]-urea

25 In a manner similar to that described in Example 2, 2-cyclopropylthiazole-4-carbonylazide (97.0 mg, 0.5 mmol) and 6-(1-methyl-pyrrolidin-2-ylmethoxy)-pyridin-2-ylamine (103.5 mg, 0.5 mmol) were heated in toluene (20 mL) to give the product as a yellow oil. MS *m/z*: 374.2 (M+H). Calc'd. for C₁₈H₂₄N₅O₂S - 374.2.

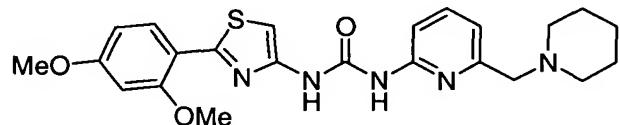
30

Example 270

5 **3-(4-{3-[6-(1-Methyl-pyrrolidin-2-ylmethoxy)-pyridin-2-yl]-ureido}-thiazol-2-yl)-benzenesulfonamide**

In a manner similar to that described in Example 2, 2-2-(3-sulfamoyl-phenyl)-thiazole-4-carbonylazide (224.0 mg, 10 0.725 mmol) and 6-(1-methyl-pyrrolidin-2-ylmethoxy)-pyridin-2-ylamine (150.0 mg, 0.725 mmol) were heated in toluene (70 mL) to give the product as a white solid. MS *m/z*: 489.2 (M+H). Calc'd. for C₂₁H₂₅N₆O₄S₂ - 489.2.

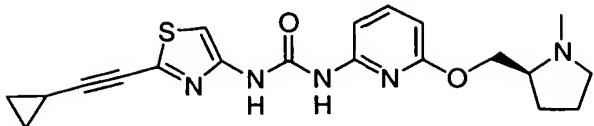
15

Example 271

20 **1-[2-(2,4-Dimethoxyphenyl)thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)urea**

The title compound was prepared by the method of Example 199. EI-MS *m/z* 454 (M+H). Calc'd for C₂₃H₂₇N₅O₃S: 453.18.

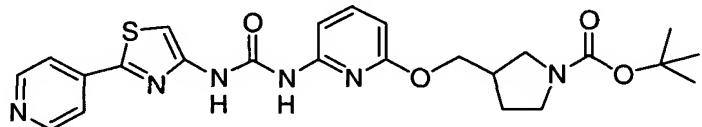
25

Example 272

5 **1-(2-Cyclopropylethynyl-thiazol-4-yl)-3-[6-(1-methyl-pyrrolidin-2-ylmethoxy)-pyridin-2-yl]-urea**

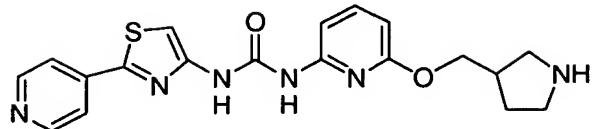
In a manner similar to that described in Example 2, 2-2-cyclopropylethynyl-thiazole-4-carbonylazide (41.4 mg, 0.190 mmol) and 6-(1-methyl-pyrrolidin-2-ylmethoxy)-pyridin-2-ylamine (47.2 mg, 0.228 mmol) were heated in toluene (1 mL) to give the product as a pale yellow solid. MS *m/z*: 398.3 (M+H). Calc'd. for C₂₀H₂₄N₅O₂S - 397.16.

15

Example 273

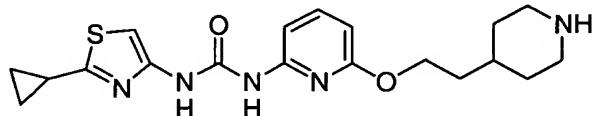
20 **tert-Butyl 3-{6-[3-(2-pyridin-4-yl-thiazol-4-yl)-ureido]-pyridin-2-ylmethoxy}-pyrrolidine-1-carboxylate**

In a manner similar to that described in Example 2, 2-2-pyridin-4-yl-thiazole-4-carbonylazide (1.927 g, 8.334 mmol) and *tert*-butyl 3-(6-amino-pyridin-2-ylmethoxy)-pyrrolidine-1-carboxylate (2.220 g, 7.577 mmol) were heated in toluene (60 mL) to give the product as a white solid. MS *m/z*: 497.0 (M+H). Calc'd. for C₂₄H₂₉N₆O₄S - 497.2.

Example 274

5 **1-(2-Pyridin-4-yl-thiazol-4-yl)-3-[6-(pyrrolidin-3-ylmethoxy)-pyridin-2-yl]-urea**

To a slurry of *tert*-butyl 3-{6-[3-(2-pyridin-4-yl-thiazol-4-yl)-ureido]-pyridin-2-yloxyethyl}-pyrrolidine-1-carboxylate (1.291 g, 2.603 mmol) in CH₂Cl₂ (25 mL) was added TFA (5 mL) under N₂. The reaction mixture was heated to reflux for 3 h, then cooled to rt. Saturated NaHCO₃ solution (40 mL) was added and the precipitate was washed with EtOAc (3 x 40 mL) and H₂O (2 x 10 mL), filtered and dried under high vacuum to give a white solid. MS *m/z*: 397.0 (M+H). Calc'd. for C₁₉H₂₁N₆O₂S - 397.1.

Example 275

20

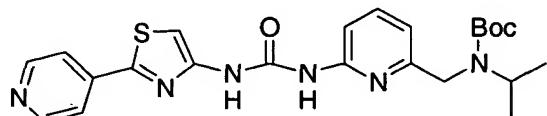
1-(2-Cyclopropyl-thiazol-4-yl)-3-[6-(2-piperidin-4-yl-ethoxy)-pyridin-2-yl]-urea

25 In a manner similar to that described in Example 2, 2-cyclopropylthiazole-4-carbonylazide (133.0 mg, 0.686 mmol) and *tert*-butyl 4-[2-(6-amino-pyridin-2-yloxy)-ethyl]-piperidine-1-carboxylate (220.0 mg, 0.686 mmol) were heated in toluene (20 mL) to give the BOC-protected product as a yellow oil. In a similar manner to Example 274, *tert*-butyl

4-(2-{6-[3-(2-cyclopropyl-thiazol-4-yl)-ureido]-pyridin-2-yloxy}-ethyl)-piperidine-1-carboxylate (7.6 mg, 0.016 mmol) was heated in CH_2Cl_2 (10 mL) in the presence of TFA (2 mL) to give the product as yellow oil. MS m/z : 388.3 ($\text{M}+\text{H}$).

5 Calc'd. for $\text{C}_{19}\text{H}_{26}\text{N}_5\text{O}_2\text{S}$ - 388.2.

Example 276



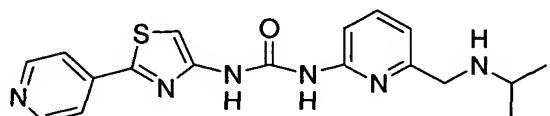
10

Isopropyl-{6-[3-(2-pyridin-4-yl-thiazol-4-yl)-ureido]-pyridin-2-ylmethyl}-carbamic acid *tert*-butyl ester

The compound was prepared in a manner similar to
 15 Example 1 using 2-pyridin-4-yl-thiazole-4-carbonyl azide and (6-amino-pyridin-2-ylmethyl)-isopropyl-carbamic acid *tert*-butyl ester to afford a white solid. MS m/z : 469.2 ($\text{M}+\text{H}$).
 Calc'd for $\text{C}_{23}\text{H}_{28}\text{N}_6\text{O}_3\text{S}$: 468.19.

20

Example 277

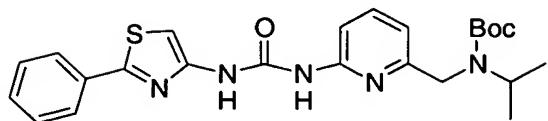


25

1-[6-(Isopropylamino-methyl)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

30

The compound was prepared in a manner similar to Example 2 to give a white solid. EI-MS m/z : 368.2 ($\text{M}+\text{H}$).
 Calc'd for $\text{C}_{18}\text{H}_{20}\text{N}_6\text{OS}$: 368.14.

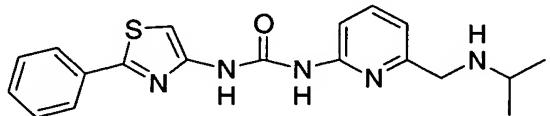
Example 278

5 **Isopropyl-{6-[3-(2-phenyl-thiazol-4-yl)-ureido]-pyridin-2-ylmethyl}-carbamic acid tert-butyl ester**

The compound was prepared in a manner similar to Example 1 using 2-phenyl-thiazole-4-carbonyl azide to afford 10 a white solid. MS m/z: 468.4 (M+H). Calc'd for C₂₄H₂₉N₅O₃S: 467.20.

Example 279

15

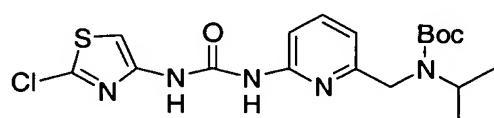


1-[6-(Isopropylamino-methyl)-pyridin-2-yl]-3-(2-phenyl-thiazol-4-yl)-urea

20

The compound was prepared in a manner similar to Example 2 to give a white solid. EI-MS m/z: 368.2 (M+H). Calc'd for C₁₉H₂₁N₅OS: 367.15.

25

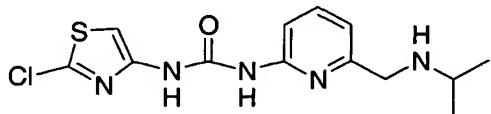
Example 280

**{6-[3-(2-Chloro-thiazol-4-yl)-ureido]-pyridin-2-ylmethyl}-
isopropyl-carbamic acid t rt-butyl ester**

The compound was prepared in a manner similar to
 5 Example 1 using 2-chloro-thiazole-4-carbonyl azide to afford
 a white solid. MS m/z: 426.3 (M+H). Calc'd for C₁₈H₂₄ClN₅O₃S: 425.13.

10

Example 281



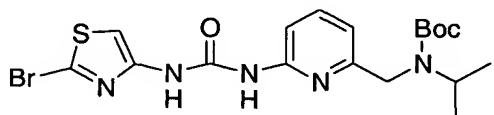
**1-(2-Chloro-thiazol-4-yl)-3-[6-(isopropylamino-methyl)-
pyridin-2-yl]-urea**

15

The compound was prepared in a manner similar to
 Example 2 to give a white solid. EI-MS m/z: 326.1 (M+H).
 Calc'd for C₁₃H₁₆ClN₅OS: 325.08.

20

Example 282

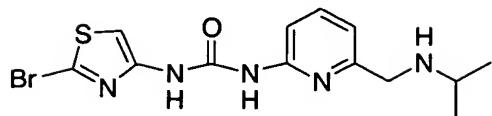


25

**{6-[3-(2-Bromo-thiazol-4-yl)-ureido]-pyridin-2-ylmethyl}-
isopropyl-carbamic acid tert-butyl ester**

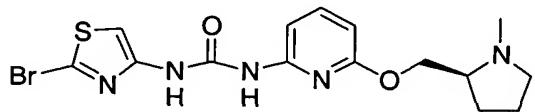
30

The compound was prepared in a manner similar to
 Example 1 to give a white solid. EI-MS m/z: 470.0 (M+H).
 Calc'd for C₁₈H₂₄BrN₅O₃S: 469.08.

Example 283

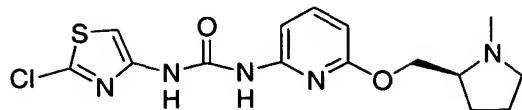
5 **1-(2-Bromo-thiazol-4-yl)-3-[6-(isopropylamino-methyl)-pyridin-2-yl]-urea**

The compound was prepared in a manner similar to Example 2 to give a white solid. EI-MS m/z: 370.2 (M+H).
 10 Calc'd for $C_{13}H_{16}BrN_5OS$: 369.03.

Example 284

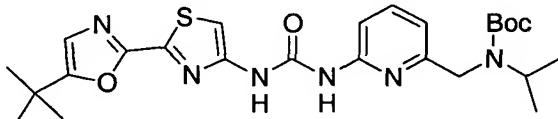
15 **1-(2-Bromo-thiazol-4-yl)-3-[6-(1-methyl-pyrrolidin-2-ylmethoxy)-pyridin-2-yl]-urea**

A stirred solution of 2-bromo-thiazole-4-carbonyl
 20 azide (0.10 g, 0.43 mmol) in dry toluene (15 mL) was heated at 85°C for 20 min followed by the addition of 6-(1-methyl-pyrrolidin-2-ylmethoxy)-pyridin-2-ylamine (0.09 g, 0.43 mmol). The resulting mixture was heated at 90°C for 15 h. The mixture was cooled to RT and concentrated. The residue
 25 obtained was washed with MeOH at RT. The impurities were dissolved in MeOH yielding a white precipitate as the desired product. MS m/z: 412.2 (M+H). Calc'd for $C_{15}H_{18}BrN_5O_2S$: 411.04.

Example 285

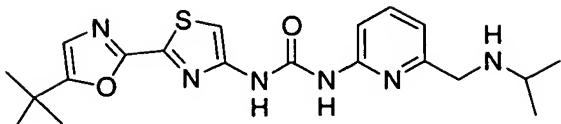
5 **1-(2-Chloro-thiazol-4-yl)-3-[6-(1-methyl-pyrrolidin-2-ylmethoxy)-pyridin-2-yl]-urea**

The compound was prepared in a manner similar to Example 15 using 2-chloro-thiazole-4-carbonyl azide to afford a white solid. EI-MS m/z: 368.2 (M+H). Calc'd for C₁₅H₁₈ClN₅O₂S: 367.09.

Example 286

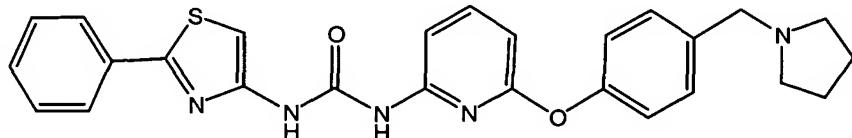
15 **(6-{3-[2-(5-tert-Butyl-oxazol-2-yl)-thiazol-4-yl]-ureido}-pyridin-2-ylmethyl)-isopropyl-carbamic acid tert-butyl ester**

20 A stirred solution of 2-(5-tert-butyl-oxazol-2-yl)-thiazole-4-carbonyl azide (0.22 g, 0.79 mmol) was heated at 85°C for 25 min followed by the addition of (6-amino-pyridin-2-ylmethyl)-isopropyl-carbamic acid tert-butyl ester. The resulting solution was heated at 90°C for 15 h. 25 The mixture was brought to RT, concentrated and purified by chromatography on silica gel using 2:1 Hexanes/EtOAc as eluent to afford a yellow solid as the desired product. MS m/z: 515.4 (M+H). Calc'd for C₂₅H₃₄N₆O₄S: 514.24.

Example 287

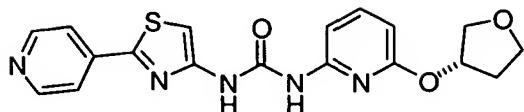
5 **1-[2-(5-tert-Butyl-oxazol-2-yl)-thiazol-4-yl]-3-[6-(isopropylamino-methyl)-pyridin-2-yl]-urea**

The compound was prepared in a manner similar to Example 2 to give a white solid. EI-MS m/z : 415.30 (M+H).
 10 Calc'd for $C_{20}H_{26}N_6O_2S$: 414.18.

Example 288

15 **1-(2-phenylthiazol-4-yl)-3-(6-pyrrolidin-1-ylmethylphenoxy)pyridin-2-yl)urea**

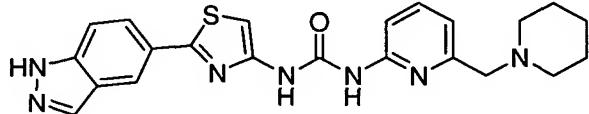
20 2-Phenyl-4-thiazolcarbonylazide (200 mg, 0.87 mmol) in dry toluene (5 mL) was heated to 105°C under N_2 and maintained at for 5 min. 2-Amino-6-(4-pyrrolidin-1-ylmethylphenoxy)pyridine was added and the resulting mixture was heated at 105°C for 4 h. After cooling to RT, the solid
 25 was filtered and rinsed with Et_2O . The product was purified by chromatography on silica gel eluting with $MeOH/CH_2Cl_2$ (5%) to form a white solid. MS m/z : 472.3 (M+H). Calc'd for $C_{26}H_{25}N_5O_2S$: 471.17.

Example 289

5 **1-(2-Pyridin-4-yl-thiazol-4-yl)-3-[6-(tetrahydro-furan-3-yloxy)-pyridin-2-yl]-urea**

In a manner similar to Example 234, 2-(4-pyridinyl)-4-thiazolcarbonylazide and 6-(Tetrahydro-furan-3-yloxy)-pyridin-2-ylamine were heated together in toluene to give 1-(2-pyridin-4-yl-thiazol-4-yl)-3-[6-(tetrahydro-furan-3-yloxy)-pyridin-2-yl]-urea as a white solid. MS *m/z*: 384.3 (M+H). Calc'd for C₁₈H₁₇N₅O₃S 383.43.

15

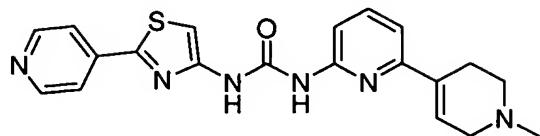
Example 290

20 **1-[2-(1H-Indazol-5-yl)-thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)-urea**

In manner similar to Example 234, 2-(1-acetyl-1H-indazol-5-yl)thiazole-4-carbonyl azide and 6-piperidin-1-ylmethyl-pyridin-2-ylamine were heated in toluene to give 1-[2-(1-acetyl-1H-indazol-5-yl)-thiazol-4-yl]-3-(6-piperidin-1-ylmethyl-pyridin-2-yl)-urea as a yellow solid (62 mg, 100%) which was next dissolved in EtOH (5 mL), treated with 1 N HCl (0.1 mL) and heated to 70°C. After 1 h, the reaction mixture was concentrated *in vacuo* and extracted with EtOAc, washed with saturated NaHCO₃, and brine, dried (MgSO₄) and concentrated *in vacuo* to give the desired

compound as a tan solid. MS m/z : 434.3 (M+H). Calc'd for $C_{22}H_{23}N_7OS$ - 433.53.

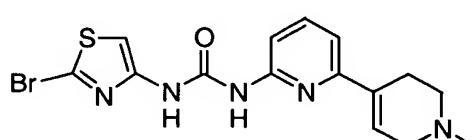
5 **Example 291**



10 **1-(1'-Methyl-1',2',3',6'-tetrahydro-[2,4']bipyridinyl-6-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)-urea**

15 In a manner similar to Example 234, 2-(4-pyridinyl)-4-thiazolcarbonylazide and 1'-methyl-1',2,3',6'-tetrahydroyo-[2,4']bipyridinyl-6yl amine were heated together in toluene to give 1-(1'-methyl-1',2',3',6'-tetrahydro-[2,4']bipyridinyl-6-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)-urea as a tan solid. MS m/z : 393.0 (M+H). Calc'd. for $C_{20}H_{20}N_6OS$ - 392.48.

20 **Example 292**

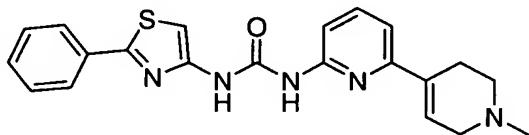


25 **1-(2-Bromo-thiazol-4-yl)-3-(1'-methyl-1',2',3',6'-tetrahydro-[2,4']bipyridinyl-6-yl)-urea**

In a manner similar to Example 234, 2-bromo-thiazole-4-carbonyl azide and 1'-methyl-1',2,3',6'-tetrahydro-[2,4']bipyridinyl-6yl amine were heated together in toluene to give 1-(2-bromo-thiazol-4-yl)-3-(1'-methyl-1',2',3',6'-tetrahydro-[2,4']bipyridinyl-6-yl)-urea as a tan solid. MS 5 m/z : 395.1 (M+H). Calc'd for $C_{15}H_{16}BrN_5OS$ - 394.29.

Example 293

10

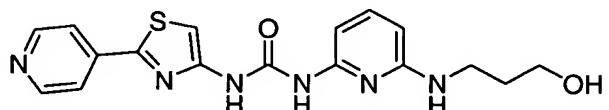


1-(1'-Methyl-1',2',3',6'-tetrahydro-2[2,4]bipyridinyl-6-yl)-3-(2-phenyl-thiazol-4-yl)-urea

15 In a manner similar to Example 234 2-phenyl-thiazole-4-carbonyl azide and 1'-methyl-1',2,3',6'-tetrahydro-[2,4']bipyridinyl-6yl amine were heated together in toluene to give 1-(1'-methyl-1',2',3',6'-tetrahydro-2[2,4]bipyridinyl-6-yl)-3-(2-phenyl-thiazol-4-yl)-urea as a 20 tan solid. MS m/z : 392.3 (M+H). Calc'd for $C_{21}H_{21}N_5OS$ 391.49.

Example 294

25

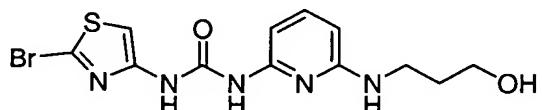


1-[6-(3-Hydroxy-propylamino)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

In a manner similar to Example 234, 2-(4-pyridinyl)-4-thiazolcarbonylazide and N-[3-(tetrahydro-pyran-2-yloxy)-propyl]-pyridine-2,6-diamine were heated together in toluene to give 1-[6-(3-hydroxy-propylamino)-pyridin-2-yl]-3-(2-pyridin-4-yl-thizol-4-yl)-urea as a yellow solid (65 mg, 16%) which was dissolved in MeOH (15 mL) and treated with 10 mg of TsOH. The reaction was heated to reflux for 2 h, quenched with saturated NaHCO₃, extracted with EtOAc, washed with brine then dried (MgSO₄) and concentrated *in vacuo* to give 1-[6-(3-hydroxy-propylamino)-pyridin-2-yl]-3-(2-pyridin-4-yl-thizol-4-yl)-urea as a yellow solid. MS *m/z*: 371.2 (M+H). Calc'd for C₁₇H₁₈N₆O₂S - 370.43.

Example 295

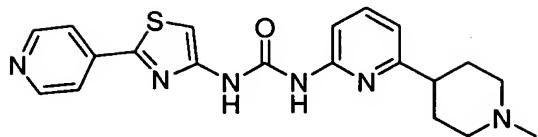
15



1-(2-Bromo-thiazol-4-yl)-3-[6-(3-hydroxy-propylamino)-pyridin-2-yl]-urea

20

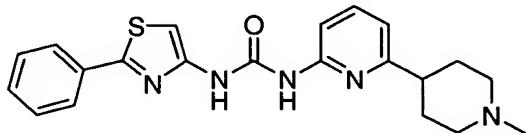
In a manner similar to example 299, 2-bromo-thiazole-4-carbonyl azide and N-[3-(tetrahydro-pyran-2-yloxy)-propyl]-pyridine-2,6-diamine were heated together in toluene to give 1-(2-bromo-thiazol-4-yl)-3-[6-(3-(tetrahydro-pyran-2-yloxy)-propylamino)-pyridin-2-yl]-urea as a yellow solid (150 mg, 75%) which was then dissolved in MeOH (15 mL) and treated with 10 mg of TsOH. Heated to reflux for 2 h, quenched with saturated NaHCO₃, extracted with EtOAc and washed with brine then dried (MgSO₄) and concentrated *in vacuo* to give 1-(2-bromo-thiazol-4-yl)-3-[6-(3-hydroxy-propylamino)-pyridin-2-yl]-urea as a white solid. MS *m/z*: 373.2 (M+H). Calc'd for C₁₂H₁₄BrN₅O₂S - 372.24.

Example 296

5

1-(1'-Methyl-1',2',3',4',5',6'-hexahydro-[2,4']bipydrinyl-6-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

In a manner similar to Example 234, 2-(4-pyridinyl)-4-thiazolcarbonylazide and 1'-methyl-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl-6-ylamine were heated together in toluene to give 1-(1'-methyl-1',2',3',4',5',6'-hexahydro-[2,4']bipydrinyl-6-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)-urea as a yellow solid. MS *m/z*: 395.0 (M+H). Calc'd. for C₂₀H₂₂N₆OS - 394.49.

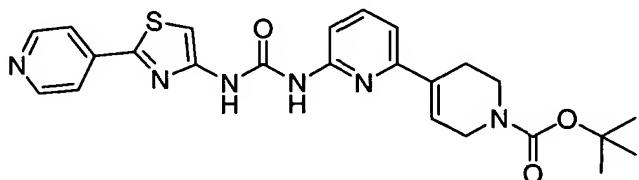
Example 297

20

1-(1'-Methyl-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl-6-yl)-3-(2-phenyl-thiazol-4-yl)-urea

In a manner similar to Example 234 2-phenyl-thiazole-4-carbonyl azide and 1'-methyl-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl-6-ylamine were heated together in toluene to give 1-(1'-methyl-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl-6-yl)-3-(2-phenyl-thiazol-4-yl)-urea as a white solid. MS m/z : 394.3 (M+H). Calc'd for $C_{21}H_{23}N_5OS$ - 393.51.

10

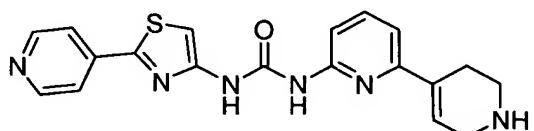
Example 298

6-[3-(2-Pyridin-4-yl-thiazol-4-yl)-ureido]-3',6'-dihydro-2'H-[2,4]bipyridinyl-1'-carboxylic acid tert-butyl ester

15

In a manner similar to Example 234, 2-(4-pyridinyl)-4-thiazolcarbonylazide and 6-amino-3',6'-dihydro-2'H-[2,4']bipyridinyl-1'-carboxylic acid tert-butyl ester were heated together in toluene to give 6-[3-(2-pyridin-4-yl-thiazol-4-yl)-ureido]-3',6'-dihydro-2'H-[2,4]bipyridinyl-1'-carboxylic acid tert-butyl ester as a yellow solid. MS m/z : 479.1 (M+H). Calc'd for $C_{24}H_{26}N_6O_3S$ 478.57.

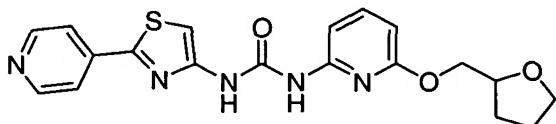
25

Example 299

1-(2-Pyridin-4-yl-thiazol-4-yl)-3-(1',2',3',6'-tetrahydro-[2,4']bipyridinyl-6-yl)-urea

6-[3-(2-Pyridin-4-yl-thizol-4-yl)-ureido]-3',6'-dihydro-2'H-[2,4]bipyridinyl-1'-carboxylic acid *tert*-butyl ester was suspended in CH₂Cl₂ (10 mL) and treated with TFA (5 mL). Stirred at RT for 30 min. Quenched with saturated NaHCO₃ and filtered yellow solid. Washed solid with H₂O and MeOH to give 1-(2-pyridin-4-yl-thiazol-4-yl)-3-(1',2',3',6'-tetrahydro-[2,4']bipyridinyl-6-yl)-urea as a yellow solid. MS *m/z*: 379.1 (M+H). Calc'd for C₁₉H₁₈N₆OS - 378.45.

10

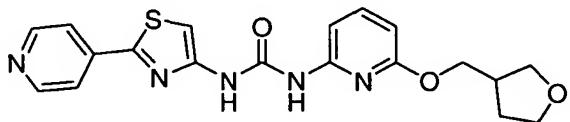
Example 300

15

1-(2-Pyridin-4-yl-thiazol-4-yl)-3-[6-(tetrahydro-furan-2-ylmethoxy)-pyridin-2-yl]-urea

In a manner similar to Example 234 2-(4-pyridinyl)-4-thiazolcarbonylazide and 6-(tetrahydro-furan-2ylmethoxy)-pyridin-2ylamine were heated together in toluene to give 1-(2-pyridin-4-yl-thiazol-4-yl)-3-[6-(tetrahydro-furan-2-ylmethoxy)-pyridin-2-yl]-urea as a yellow solid. MS *m/z*: 398.4 (M+H). Calc'd for C₁₉H₁₉N₅O₃S - 397.45.

25

Example 301

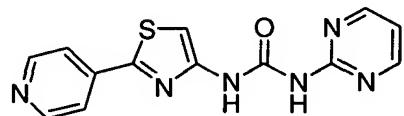
30

1-(2-Pyridin-4-yl-thizol-4-yl)-3-[6-(tetrahydro-furan-3-ylmethoxy)-pyridin-2-yl]-urea

In a manner similar to Example 234, 2-(4-pyridinyl)-4-thiazolcarbonylazide and 6-(tetrahydro-furan-3ylmethoxy)-pyridin-2ylamine were heated together in toluene to give 1-(2-pyridin-4-yl-thiazol-4-yl)-3-[6-(tetrahydro-furan-3-ylmethoxy)-pyridin-2-yl]-urea as a yellow solid. MS *m/z*: 398.3 (M+H). Calc'd. for $C_{19}H_{19}N_5O_3S$ - 397.45.

Example 302

10

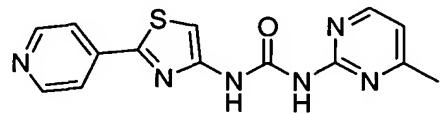


1-(2-Pyridin-4-yl-thiazol-4-yl)-3-pyrimidin-2-yl-urea

15 In a manner similar to Example 234 2-(4-pyridinyl)-4-thiazolcarbonylazide and 2-aminopyrimidine were heated together in toluene to give 1-(2-pyridin-4-yl-thiazol-4-yl)-3-pyrimidin-2-yl-urea as a yellow solid. MS *m/z*: 299.1 (M+H). Calc'd for $C_{13}H_{10}N_6OS$ - 298.32.

20

Example 303



25 1-(4-Methyl-pyrimidin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

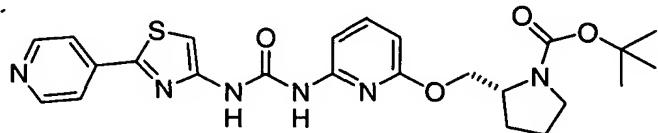
30 In a manner similar to Example 234, 2-(4-pyridinyl)-4-thiazolcarbonylazide and 2-amino-4-methyl-pyrimidine were heated together in toluene to give 1-(4-methyl-pyrimidin-2-

yl)-3-(2-pyridin-4-yl-thiazol-4-yl)-urea as a yellow solid.

MS *m/z*: 313.1 (M+H). Calc'd for C₁₄H₁₂N₆OS 312.35.

Example 304

5



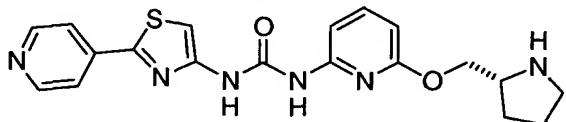
2-[6-[3-(2-Pyridin-4-yl-thiazol-4-yl)-ureido]-pyridin-2-yloxy]methyl]pyrrolidine-1-carboxylic acid *tert*-butyl ester

10

In a manner similar to Example 234, 2-(4-pyridinyl)-4-thiazolcarbonylazide and 2-(6-amino-pyridin-2-yloxy)methyl]pyrrolidine-1-carboxylic acid *tert*-butyl ester were heated together in toluene to give 1-(2-pyridin-4-yl-thiazol-4-yl)-3-[6-(tetrahydro-furan-3-yloxy)-pyridin-2-yl]-urea as a yellow solid. MS *m/z*: 497.4 (M+H). Calc'd for C₂₄H₂₈N₆O₄S - 496.58.

Example 305

20



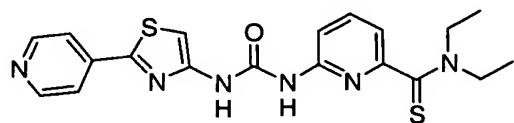
1-(2-Pyridin-4-yl-thiazol-4-yl)-3-[6-(pyrrolidin-2-ylmethoxy)-pyridin-2-yl]-urea

25

To a solution of 1-(2-pyridin-4-yl-thiazol-4-yl)-3-[6-(tetrahydro-furan-3-yloxy)-pyridin-2-yl]-urea and 150 ml of CH₂Cl₂ was added 50 mL of TFA. Stirred at RT for 30 min, then concentrated *in vacuo*. Neutralized with saturated NaHCO₃ and basified to pH 9. Filtered white precipitate and washed with H₂O and Et₂O. Dried on high-vacuum to give 1-

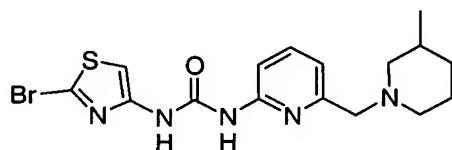
(2-pyridin-4-yl-thiazol-4-yl)-3-[6-(pyrrolidin-2-ylmethoxy)-pyridin-2-yl]-urea as an off-white solid. MS m/z : 497.4 (M+H). Calc'd for $C_{19}H_{20}N_6O_2S$ - 396.47.

5

Example 306

10 **6-[3-(2-Pyridin-4-yl-thiazol-4-yl)-ureido]-pyridine-2-carbothioic acid diethylamide**

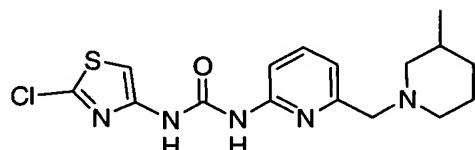
MS m/z : 413.0 (M+H). Calc'd. for $C_{19}H_{20}N_6OS_2$ - 412.11.

Example 307

15

1-(2-Bromo-thiazol-4-yl)-3-[6-(3-methyl-piperidin-1-ylmethylethyl)-pyridin-2-yl]-urea

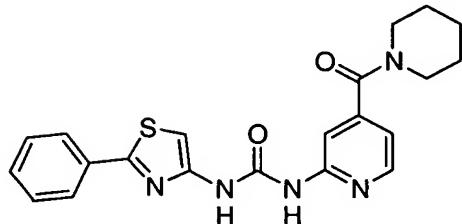
20 MS m/z : 410.3 (M+H). Calc'd. for $C_{16}H_{20}BrN_5OS$ - 409.06.

Example 308

25 **1-(2-Chloro-thiazol-4-yl)-3-[6-(3-methyl-piperidin-1-ylmethylethyl)-pyridin-2-yl]-urea**

MS *m/z*: 366.2 (M+H). Calc'd. for C₁₆H₂₀ClN₅OS - 365.1.

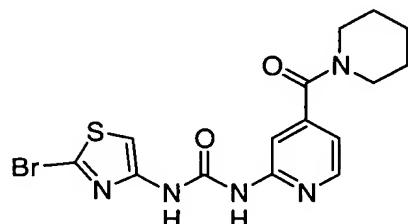
Example 309



1-(2-Phenyl-thiazol-4-yl)-3-[4-(piperidine-1-carbonyl)-pyridin-2-yl]-urea

10 MS *m/z*: 408.3 (M+H). Calc'd for C₂₁H₂₁N₅O₂S - 407.49.

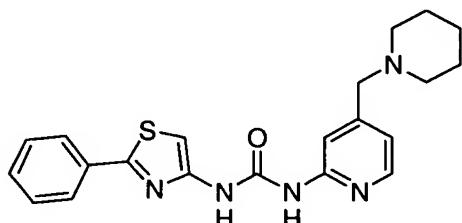
Example 310



1-(2-Bromo-thiazol-4-yl)-3-[4-(piperidine-1-carbonyl)-pyridin-2-yl]-urea

20 MS *m/z*: 412.0 (M+2H). Calc'd for C₁₅H₁₆BrN₅O₂S - 410.29.

Example 311

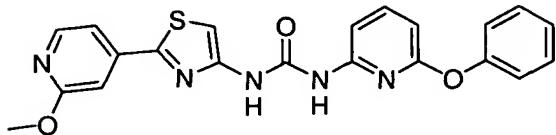


1-(2-Phenyl-thiazol-4-yl)-3-(4-piperidin-1-ylmethyl-pyridin-2-yl)-urea

MS *m/z*: 394.3 (M+H). Calc'd for C₂₁H₂₃N₅OS - 393.51.

Example 312

5



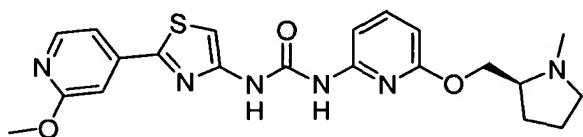
1-[2-(2-Methoxy-pyridin-4-yl)-thiazol-4-yl]-3-(6-phenoxy-pyridin-2-yl)-urea

10

MS *m/z*: 420.1 (M+H). Calc'd for C₂₁H₁₇N₅O₃S - 419.46.

Example 313

15



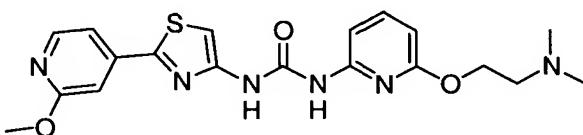
1-[2-(2-Methoxy-pyridin-4-yl)-thiazol-4-yl]-3-[6-(1-methyl-pyrrolidin-2-ylmethoxy)-pyridin-2-yl]-urea

20

MS *m/z*: 441.0 (M+H). Calc'd for C₂₁H₂₄N₆O₃S - 440.52.

Example 314

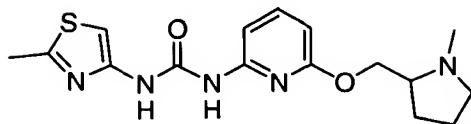
25



1-[6-(2-Dimethylamino-ethoxy)-pyridin-2-yl]-3-[2-(2-methoxy-pyridin-4-yl)-thiazol-4-yl]-urea

30

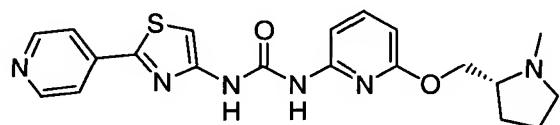
MS *m/z*: 415.0 (M+H). Calc'd for C₁₉H₂₂N₆O₃S - 414.48.

Example 318

5 **1-[6-(1-Methyl-pyrrolidin-2-ylmethoxy)-pyridin-2-yl]-3-(2-methyl-thiazol-4-yl)-urea**

MS *m/z*: 348.1 (M+H). Calc'd for C₁₆H₂₁N₅O₂S - 347.44.

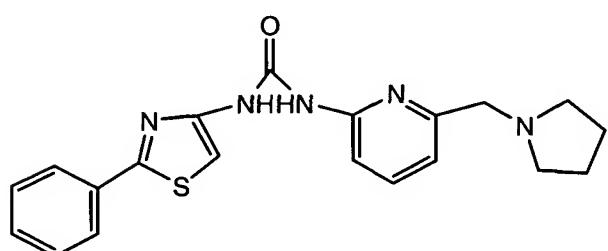
10

Example 316

15 **1-[6-(1-Methyl-pyrrolidin-2-ylmethoxy)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea**

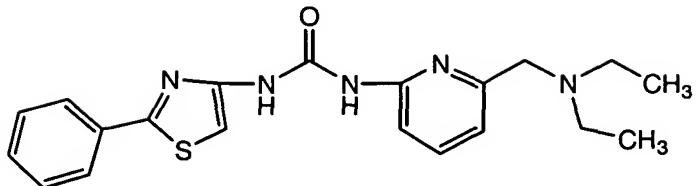
MS *m/z*: 411.1 (M+H). Calc'd for C₂₀H₂₂N₆O₂S - 410.49.

20

Example 317

1-(2-phenylthiazol-4-yl)-3-(6-pyrrolidin-1-ylmethyl-pyridin-2-yl)urea

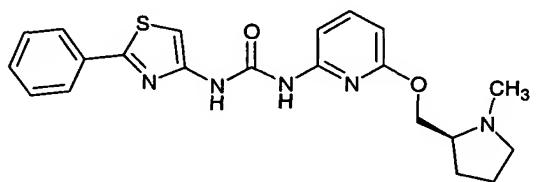
25 EI-MS *m/z* 380.4 (M+H). Calc'd for C₂₀H₂₁N₅OS: 379.15.

Example 318

5 **1-(6-Diethylaminomethylpyridin-2-yl)-3-(2-phenylthiazol-4-yl)urea**

EI-MS m/z 382.2 (M+H). Calc'd for C₂₀H₂₃N₅OS: 381.16.

10

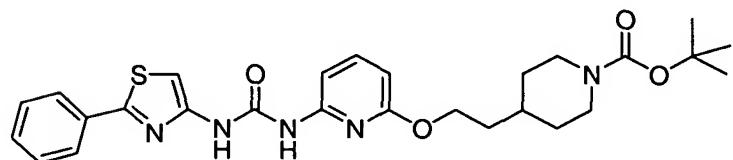
Example 319

15 **(S)-1-[6-(1-Methylpyrrolidin-2-ylmethoxy)pyridin-2-yl]-3-(2-phenylthiazol-4-yl)urea**

EI-MS m/z 410.0 (M+H). Calc'd for C₂₁H₂₃N₅O₂S: 409.16.

Example 320

20



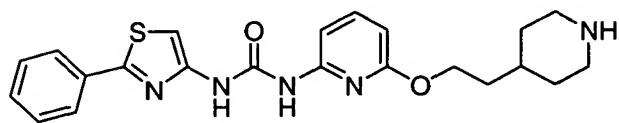
tert-Butyl 4-(2-{3-(2-phenylthiazol-4-yl)-ureido}pyridin-2-yl)ethyl)piperidine-1-carboxylate

25

MS *m/z*: 524.3 (M+H). Calc'd for C₂₇H₃₃N₅O₄S: 523.23

Example 321

5



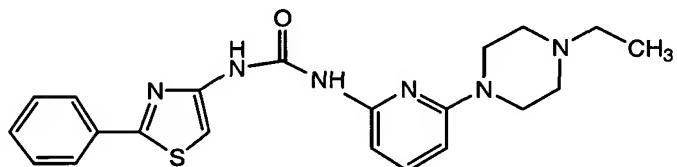
1-[6-(2-Piperidin-4-yl-ethoxy)pyridin-2-yl]-3-[2-phenylthiazol-4-yl]urea

10

MS *m/z*: 424.1 (M+1). Calc'd for C₂₂H₂₅N₅O₂S: 423.17.

Example 322

15

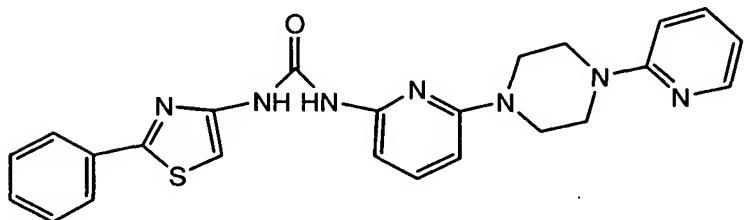


1-[6-(4-Ethylpiperazin-1-yl)-pyridin-2-yl]-3-(2-phenylthiazol-4-yl)urea

20

EI-MS *m/z* 419.3 (M+H). Calc'd for C₂₁H₂₄N₆OS: 408.17.

Example 323

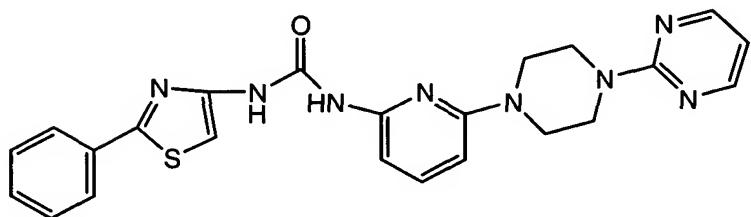


1-[6-(4-Pyridin-2-yl-piperazin-1-yl)pyridin-2-yl]-3-(2-
ph nylthiazol-4-yl)ur a

EI-MS m/z 458.2 (M+H). Calc'd for C₂₄H₂₃N₇OS: 457.17.

5

Example 324

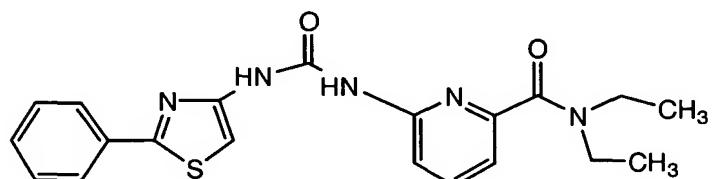


10 1-(2-phenylthiazol-4-yl)-3-[6-(4-pyrimidin-2-yl-piperazin-1-
y1)pyridin-2-yl]urea

EI-MS m/z 459.4 (M+H). Calc'd for C₂₃H₂₂N₈OS: 458.16.

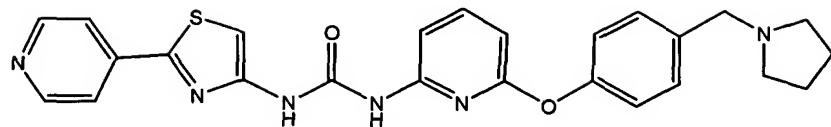
15

Example 325



20 Diethyl 6-[3-(2-phenylthiazol-4-yl)ureido]-pyridine-2-
carboxamide

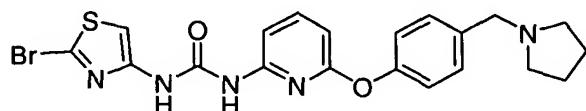
EI-MS m/z 396.3 (M+H). Calc'd for C₂₀H₂₁N₅O₂S: 395.14.

Example 326

5 **1-(2-Pyridin-4-yl-thiazol-4-yl)-3-(6-pyrrolidin-1-ylmethylphenoxy)pyridin-2-yl)urea**

EI-MS m/z 473.3 (M+H). Calc'd for C₂₅H₂₄N₆O₂S: 472.17.

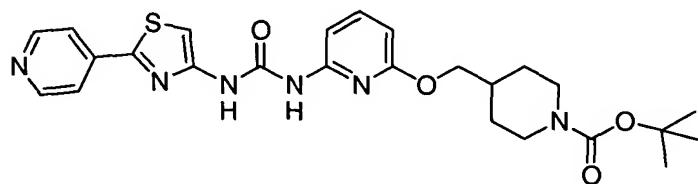
10

Example 327

15 **1-(2-Bromothiazol-4-yl)-3-(6-pyrrolidin-1-ylmethylphenoxy)pyridin-2-yl)urea**

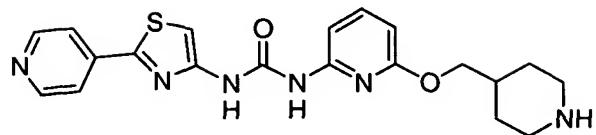
MS m/z: 473.9 (M+H). Calc'd for C₂₀H₂₀BrN₅O₂S: 473.05.

20

Example 328

25 **4-{6-[3-(2-Pyridin-4-yl-thiazol-4-yl)-ureido]pyridin-2-yloxymethyl}-piperidine-1-carboxylic acid tert-butyl ester**

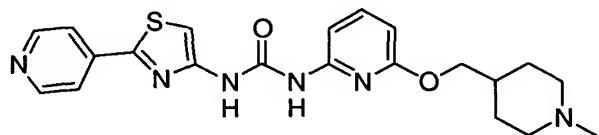
MS m/z: 511.2 (M+H). Calc'd for C₂₅H₃₀N₆O₄S - 510.61.

Example 329

5 **1-[6-(Piperidin-4-ylmethoxy)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea**

MS m/z: 411.0 (M+H). Calc'd for C₂₀H₂₂N₆O₂S - 410.49.

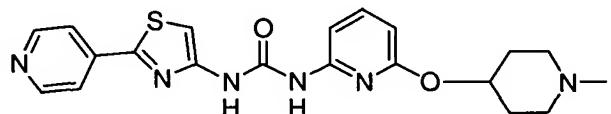
10

Example 330

15 **1-[6-(1-Methyl-piperidin-4-ylmethoxy)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea**

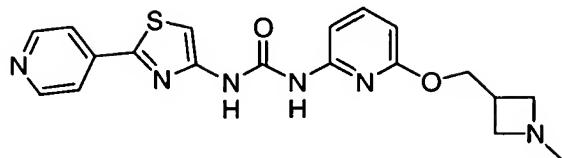
MS m/z: 425.2 (M+H). Calc'd for C₂₁H₂₄N₆O₂S - 424.52.

20

Example 331

25 **1-[6-(1-Methyl-piperidin-4-yloxy)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea**

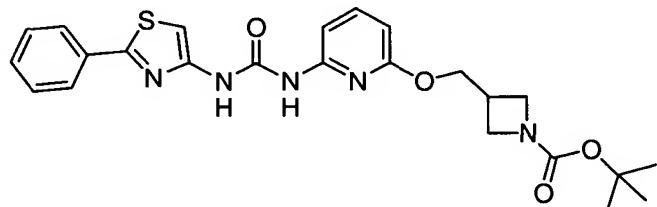
MS m/z: 411.0 (M+H). Calc'd for C₂₀H₂₂N₆O₂S - 410.49.

Example 332

5 **1-[6-(1-Methyl-azetidin-3-ylmethoxy)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea**

MS m/z: 397.3 (M+H). Calc'd for C₁₉H₂₀N₆O₂S - 396.47.

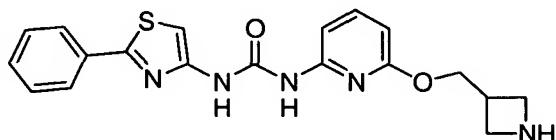
10

Example 333

15 **3-{6-[3-(2-Phenyl-thiazol-4-yl)-ureido]-pyridin-2-yl}oxymethyl-azetidine-1-carboxylic acid tert-butyl ester**

MS m/z: 482.4 (M+H). Calc'd for C₂₄H₂₇N₅O₄S - 481.57.

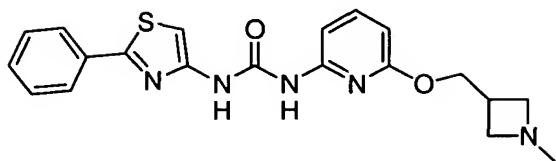
20

Example 334

1-[6-(Azetidin-3-ylmethoxy)-pyridin-2-yl]-3-(2-phenyl-thiazol-4-yl)-urea

25

MS m/z: 382.3 (M+H). Calc'd for C₁₉H₁₉N₅O₂S - 381.45.

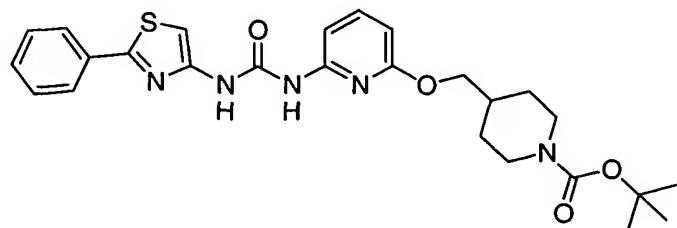
Example 335

5

1-[6-(1-Methyl-azetidin-3-ylmethoxy)-pyridin-2-yl]-3-(2-phenyl-thiazol-4-yl)-urea

MS m/z: 396.3 (M+H). Calc'd for C₂₀H₂₁N₅O₂S ~ 395.48.

10

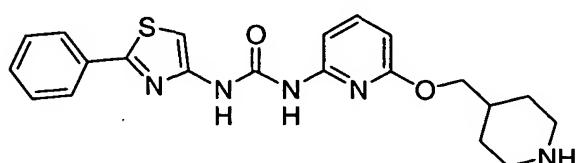
Example 336

15

4-{6-[3-(2-Phenyl-thiazol-4-yl)-ureido]-pyridin-2-yl}-1-methoxy-1-oxymethyl-piperidine-1-carboxylic acid tert-butyl ester

MS m/z: 510.3 (M+H). Calc'd for C₂₆H₃₁N₅O₄S ~ 509.62.

20

Example 337

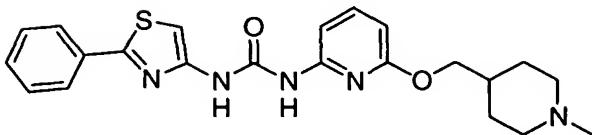
25

1-(2-Phenyl-thiazol-4-yl)-3-[6-(piperidin-4-ylmethoxy)-pyridin-2-yl]-urea

MS m/z: 410.3 (M+H). Calc'd for C₂₁H₂₃N₅O₄S - 409.51.

Example 338

5



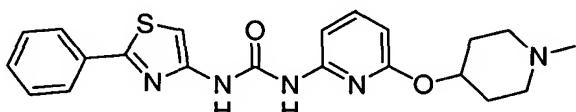
1-[6-(1-Methyl-piperidin-4-ylmethoxy)-pyridin-2-yl]-3-(2-phenyl-thiazol-4-yl)-urea

10

MS m/z: 424.2 (M+H). Calc'd for C₂₂H₂₅N₅O₂S - 423.53.

Example 339

15



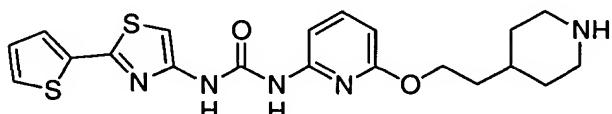
1-[6-(1-Methyl-piperidin-4-yloxy)-pyridin-2-yl]-3-(2-phenyl-thiazol-4-yl)-urea

20

MS m/z: 410.4 (M+H). Calc'd for C₂₁H₂₃N₅O₂S - 409.51.

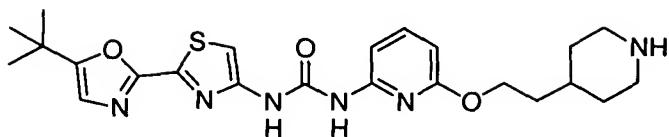
Example 340

25



1-[6-(2-Piperidin-4-yl-ethoxy)-pyridin-2-yl]-3-(2-thiophen-2-yl-thiazol-4-yl)-urea

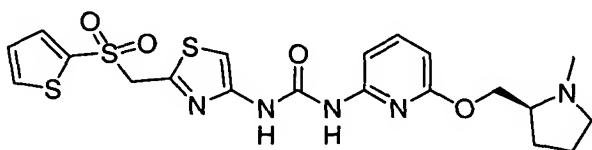
MS m/z: 430.1 (M+H). Calc'd for C₂₀H₂₃N₅O₂S₂ - 429.56.

Example 341

5 **1-[2-(5-tert-Butyl-oxazol-2-yl)-thiazol-4-yl]-3-[6-(2-piperidin-4-yl-ethoxy)-pyridin-2-yl]-urea**

MS m/z: 471.1 (M+H). Calc'd for C₂₃H₃₀N₆O₃S - 470.59.

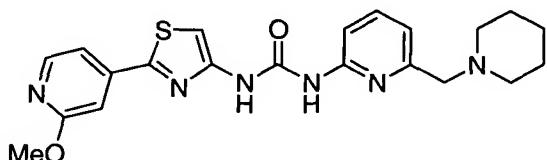
10

Example 342

15 **1-[6-(1-Methyl-pyrrolidin-2-ylmethoxy)-pyridin-2-yl]-3-[2-(thiophene-2-sulfonylmethyl)-thiazol-4-yl]-urea**

MS m/z: 494.0 (M+H). Calc'd for C₂₀H₂₃N₅O₄S₃ - 493.63.

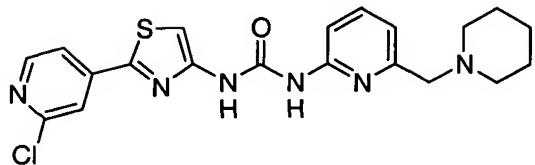
20

Example 343

1-[2-(2-Methoxy-pyridin-4-yl)-thiazol-4-yl]-3-(6-piperdin-1-ylmethoxy-pyridin-2-yl)-urea

25

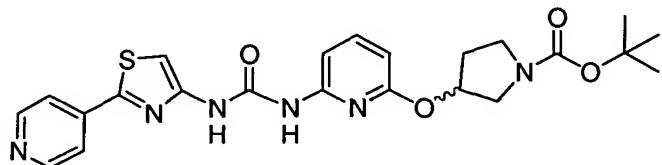
MS m/z: 425.1 (M+H). Calc'd for C₂₁H₂₄N₆O₂S - 424.52.

Example 344

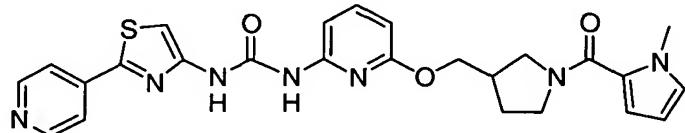
5 **[2-(2-Chloropyridin-4-yl)-thiazol-4-yl]-3-(6-piperdin-1-ylmethyl-pyridin-2-yl)-urea**

MS *m/z*: 429.1 (M+H). Calc'd for C₂₀H₂₁ClN₆OS - 428.9.

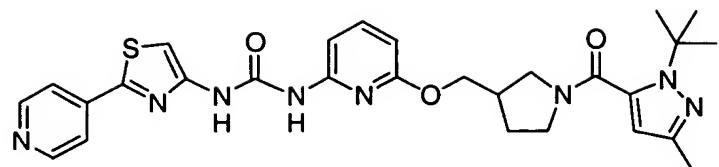
10 The following compounds can be made by procedures similar to those previously described:



15 **tert-Butyl 3-{6-[3-(2-pyridin-4-yl-thiazol-4-yl)-ureido]-pyridin-2-yloxy}-pyrrolidine-1-carboxylate**

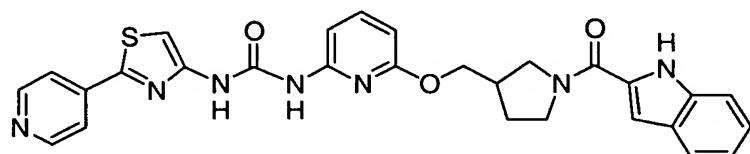


20 **1-{6-[1-(1-Methyl-1H-pyrrole-2-carbonyl)-pyrrolidin-3-ylmethoxy]-pyridin-2-yl}-3-(2-pyridin-4-yl-thiazol-4-yl)-urea**



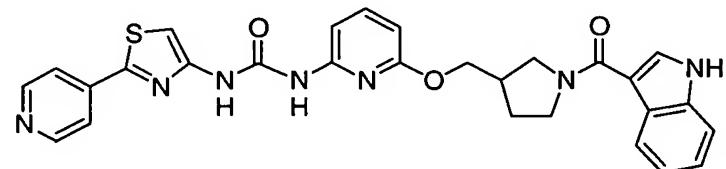
5

1-[6-[1-(2-tert-Butyl-5-methyl-2H-pyrazole-3-carbonyl)-pyrrolidin-3-ylmethoxy]-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea



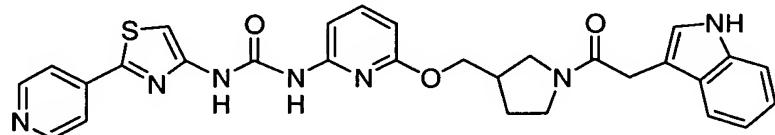
10

1-[6-[1-(1H-Indole-2-carbonyl)-pyrrolidin-3-ylmethoxy]-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea



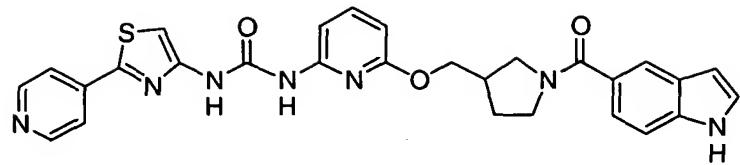
15

1-[6-[1-(1H-Indole-3-carbonyl)-pyrrolidin-3-ylmethoxy]-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

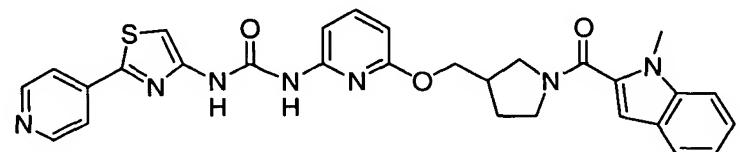


20

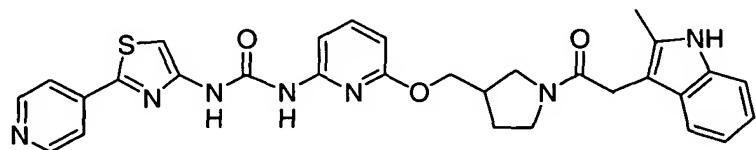
1-[6-[1-(2-1H-Indol-3-yl-acetyl)-pyrrolidin-3-ylmethoxy]-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea



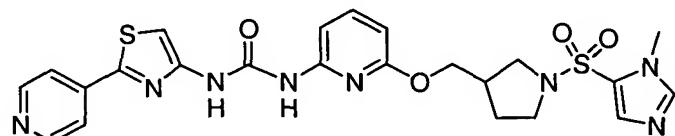
5 1-[6-[1-(1H-Indole-5-carbonyl)-pyrrolidin-3-ylmethoxy]-
pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea



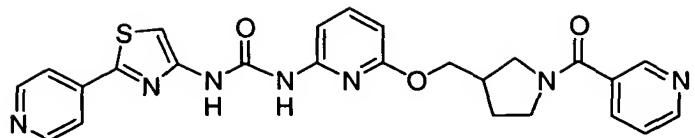
10 1-[6-[1-(1-Methyl-1H-indole-2-carbonyl)-pyrrolidin-3-
ylmethoxy]-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-
urea



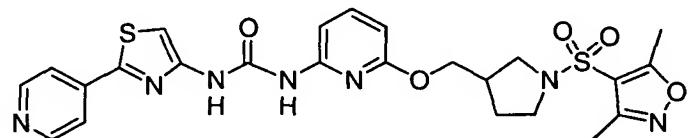
15 1-(6-{1-[2-(2-Methyl-1H-indol-3-yl)-acetyl]-pyrrolidin-3-
ylmethoxy}-pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)-
urea



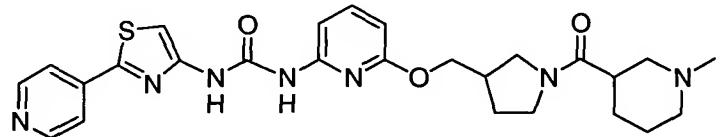
20 1-[6-[1-(3-Methyl-3H-imidazole-4-sulfonyl)-pyrrolidin-3-
ylmethoxy]-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-
urea



5 1-[6-[1-(Pyridine-3-carbonyl)-pyrrolidin-3-ylmethoxy]-
pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

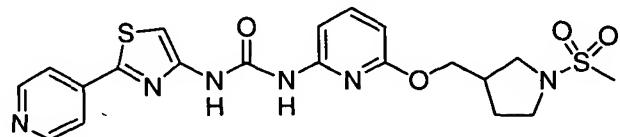


10 1-[6-[1-(3,5-Dimethyl-isoxazole-4-sulfonyl)-pyrrolidin-3-
ylmethoxy]-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-
urea

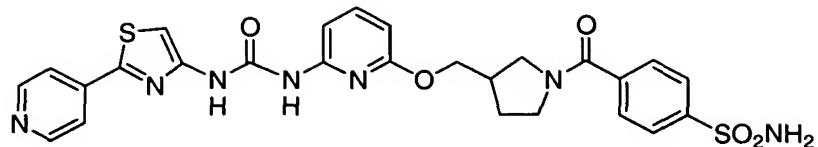


15 1-[6-[1-(1-Methyl-piperidine-3-carbonyl)-pyrrolidin-3-
ylmethoxy]-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-
urea

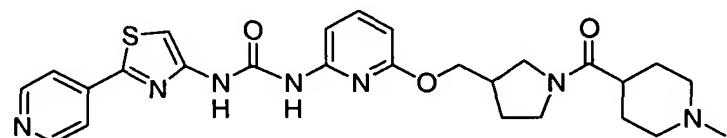
20



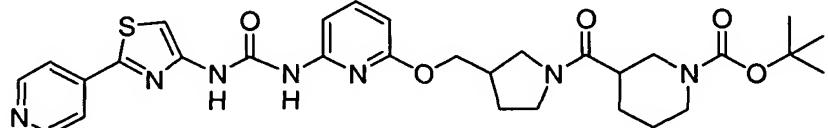
20 1-[6-(1-M thanesulfonyl-pyrrolidin-3-ylmethoxy)-pyridin-2-
yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea



5 **4-(3-{6-[3-(2-Pyridin-4-yl-thiazol-4-yl)-ureido]-pyridin-2-yloxy-methyl}-pyrrolidine-1-carbonyl)-benzenesulfonamide**



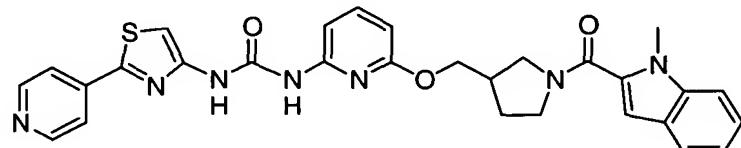
10 **1-{6-[1-(1-Methyl-piperidine-4-carbonyl)-pyrrolidin-3-ylmethoxy]-pyridin-2-yl}-3-(2-pyridin-4-yl-thiazol-4-yl)-urea**



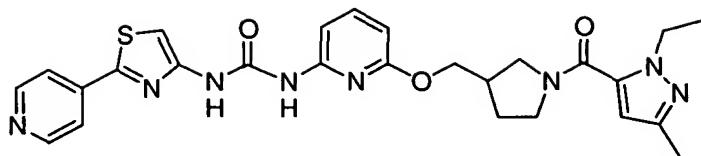
15

tert-Butyl 3-(3-{6-[3-(2-pyridin-4-yl-thiazol-4-yl)-ureido]-pyridin-2-yloxy-methyl}-pyrrolidine-1-carbonyl)-piperidine-1-carboxylate

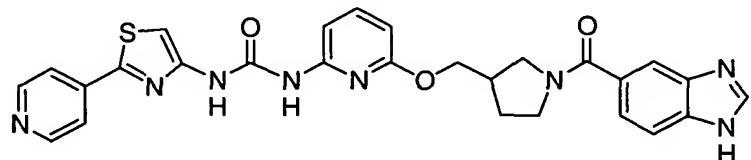
20



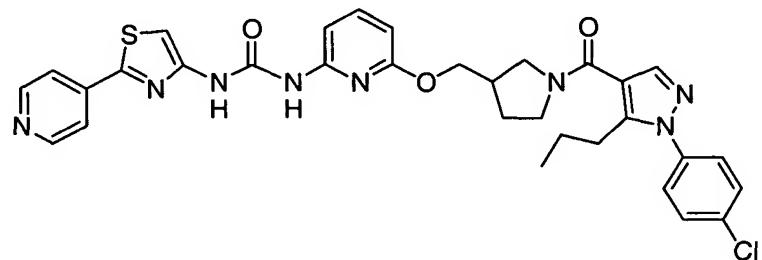
1-{6-[1-(1-Methyl-1H-indole-2-carbonyl)-pyrrolidin-3-ylmethoxy]-pyridin-2-yl}-3-(2-pyridin-4-yl-thiazol-4-yl)-urea



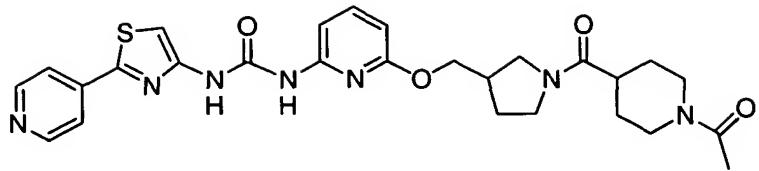
5 **1-[6-[1-(2-Ethyl-5-methyl-2H-pyrazole-3-carbonyl)-pyrrolidin-3-ylmethoxy]-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea**



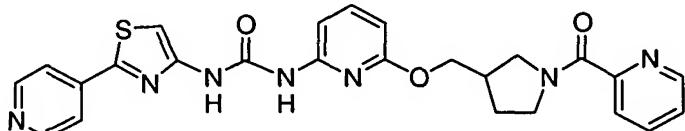
10 **1-[6-[1-(1H-Benzimidazole-5-carbonyl)-pyrrolidin-3-ylmethoxy]-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea**



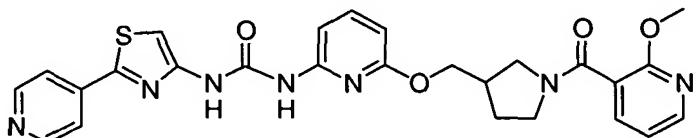
15 **1-[6-{1-[1-(4-Chlorophenyl)-5-propyl-1H-pyrazole-4-carbonyl]-pyrrolidin-3-ylmethoxy}-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea**



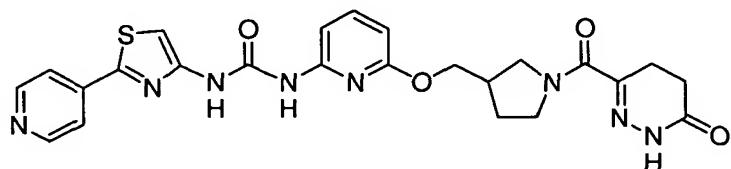
5 1-[6-[1-(1-Acetyl-piperidine-4-carbonyl)-pyrrolidin-3-ylmethoxy]-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea



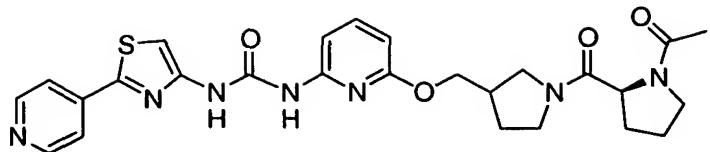
10 1-[6-[1-(Pyridine-2-carbonyl)-pyrrolidin-3-ylmethoxy]-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea



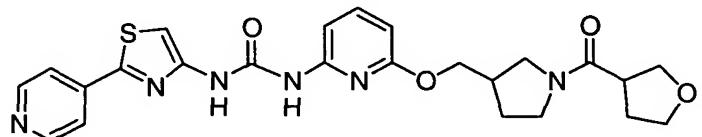
15 1-[6-[1-(2-Methoxy-pyridine-3-carbonyl)-pyrrolidin-3-ylmethoxy]-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea



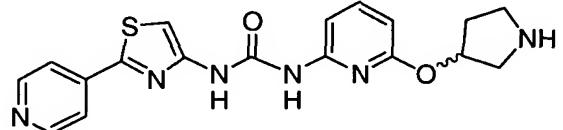
20 1-[6-[1-(6-Oxo-1,4,5,6-tetrahydro-pyridazine-3-carbonyl)-pyrrolidin-3-ylmethoxy]-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea



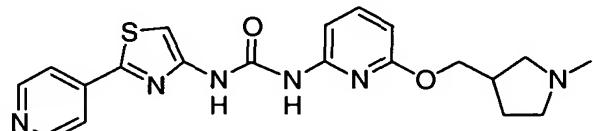
5 **1-{6-[1-(1-Acetyl-pyrrolidine-2-carbonyl)-pyrrolidin-3-ylmethoxy]-pyridin-2-yl}-3-(2-pyridin-4-yl-thiazol-4-yl)-urea**



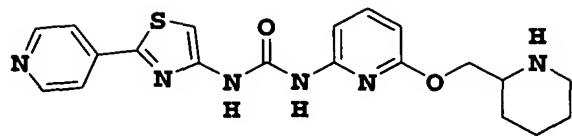
10 **1-(2-Pyridin-4-yl-thiazol-4-yl)-3-{6-[1-(tetrahydro-furan-3-carbonyl)-pyrrolidin-3-ylmethoxy]-pyridin-2-yl}-urea**



15 **1-(2-Pyridin-4-yl-thiazol-4-yl)-3-[6-(pyrrolidin-3-ylxy)-pyridin-2-yl]-urea**

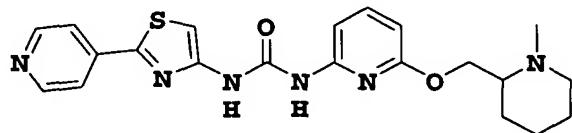


20 **1-[6-(1-Methyl-pyrrolidin-3-ylmethoxy)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea**



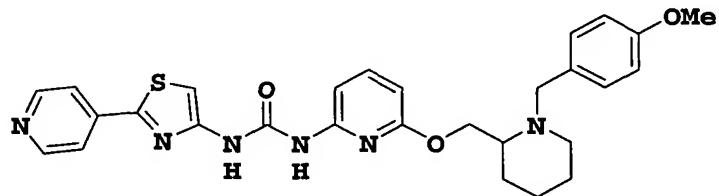
1-[6-(Piperidin-2-ylmethoxy)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

5



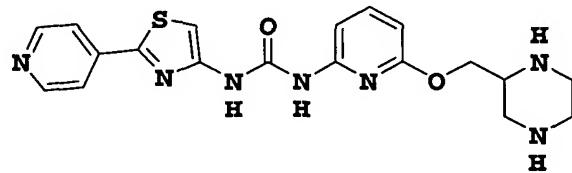
1-[6-(1-Methyl-piperidin-2-ylmethoxy)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

10



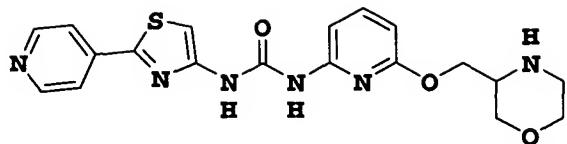
1-[6-[1-(4-Methoxy-benzyl)-piperidin-2-ylmethoxy]-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

15



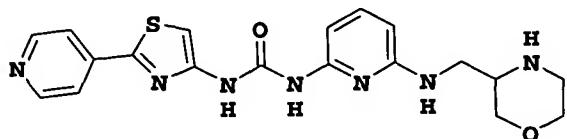
1-[6-(Piperazin-2-ylmethoxy)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

20



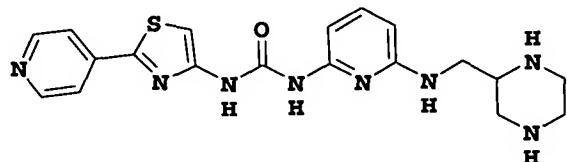
1-[6-(Morpholin-3-ylmethoxy)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

5



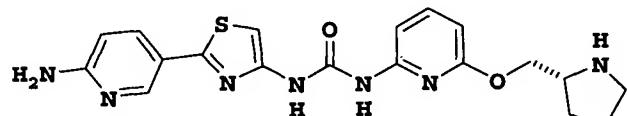
1-[6-[(Morpholin-3-ylmethyl)-amino]-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

10



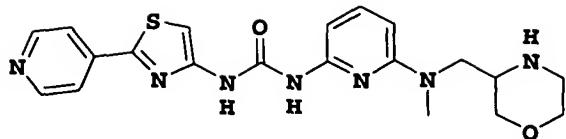
1-[6-[(Piperazin-2-ylmethyl)-amino]-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

15



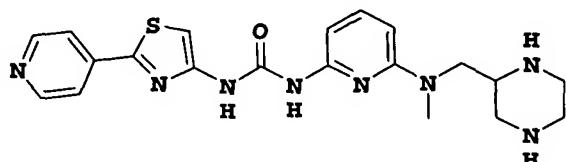
1-[2-(6-Amino-pyridin-3-yl)-thiazol-4-yl]-3-[6-(pyrrolidin-2-ylmethoxy)-pyridin-2-yl]-urea

20



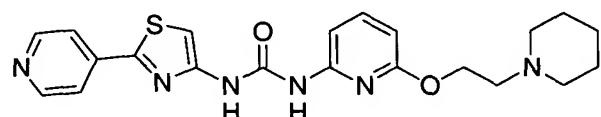
1-[6-(Methyl-morpholin-3-ylmethyl-amino)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

5



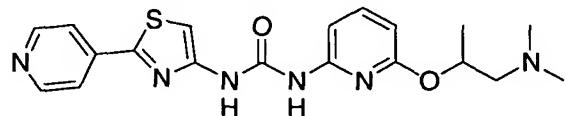
1-[6-(Methyl-piperazin-2-ylmethyl-amino)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

10



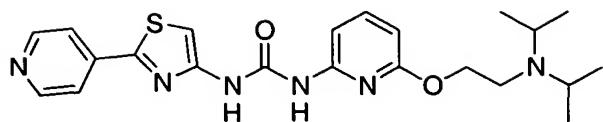
1-[6-(2-Piperidin-1-yl-ethoxy)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

15



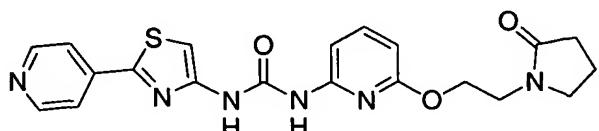
1-[6-(2-Dimethylamino-1-methyl-ethoxy)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

20



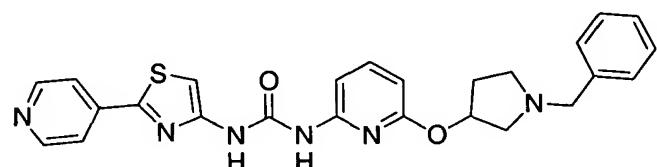
1-[6-(2-Diisopropylamino-ethoxy)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

5



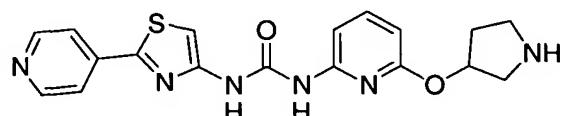
1-[6-[2-(2-Oxo-pyrrolidin-1-yl)-ethoxy]-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

10



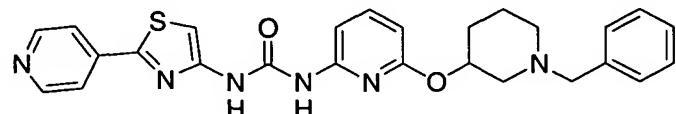
1-[6-(1-Benzyl-pyrrolidin-3-ylloxy)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

15

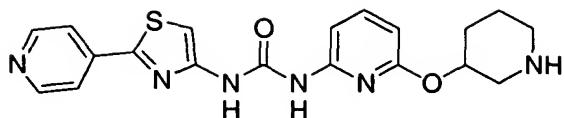


1-(2-Pyridin-4-yl-thiazol-4-yl)-3-[6-(pyrrolidin-3-ylloxy)-pyridin-2-yl]-urea

20

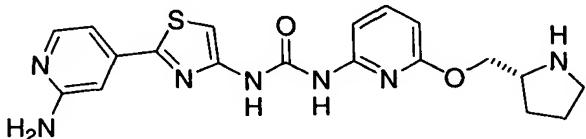


1-[6-(1-Benzyl-piperidin-3-ylloxy)-pyridin-2-yl]-3-(2-pyridin-4-yl-thiazol-4-yl)-urea



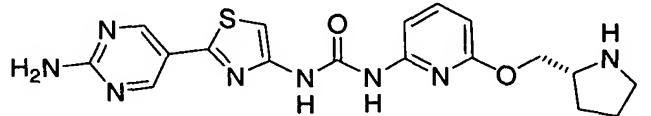
1-[(6-(Piperidin-3-yloxy)-pyridin-2-yl)-3-(2-pyridin-4-yl-thiazol-4-yl)-urea

5



1-[(2-(2-Amino-pyridin-4-yl)-thiazol-4-yl)-3-(6-(pyrrolidin-2-ylmethoxy)-pyridin-2-yl)-urea

10



15

1-[(2-(2-Amino-pyrimidin-5-yl)-thiazol-4-yl)-3-(6-(pyrrolidin-2-ylmethoxy)-pyridin-2-yl)-urea.

20

The pharmacological properties of the compounds of this invention may be confirmed by a number of pharmacological assays. The exemplified pharmacological assays which follow have been carried out with the compounds according to the invention and their salts. The compounds of invention exhibited more than 10% cdk5/p25 or cdk2/cyclin inhibition at 10 μ M.

25

BIOLOGICAL EVALUATION**PROTOCOLS FOR CYCLIN E2/CDK2**5 Cloning of Cdk2 and cyclin 2/Generation of Cdk2 and cyclin 2 Recombinant Baculovirus

The following oligonucleotide primers flanking the coding sequence of the human Cdk2 cDNA clone were used to amplify the gene and place EcoRI and HindIII restriction sites at the 5' and 3' ends of the gene respectively. [5' oligo-5'-AAGCGCGCGAATTCTATAAATATGGAGAACTTCCAAAAGGTGGAA-3'; 3' oligo-5'-CTCGACAAGCTTATTAGAGTCGAAGATGGGTAC-3']

15 The following oligonucleotide primers flanking the coding sequence of the human CycE2 cDNA clone were used to amplify the gene and place XhoI and SphI restriction sites at the 5' and 3' ends of the gene respectively. A His tag was also placed at the N-terminus of the CycE2 protein. [5' oligo-5'-

20 CCCGGGATCTCGAGATAAAATATGCATCATCATCATCATTCAAGACGAAGTAGCCGTTAC AA -3'; 3' oligo-5'-CCCGGTACCGCATGCTTAGTGTCTCCTGGTGGTTTC -3']

25 CycE-2 and Cdk2 PCR fragments were subcloned into the vector pFastBacDual (Gibco/LifeTechnologies) using the restriction sites indicated above. Recombinant virus was made following protocols supplied by the manufacturer.

Expression of cyclin 2/CDK2 in insect cells

30 Hi5 cells were grown to a cell density of 1×10^6 cells per ml in 800 ml of Excell 405 media (JRH). Cells were infected with virus at a multiplicity of 1. Infected cultures were incubated with shaking at 28°C. Cells were harvested by centrifugation.

Cloning of Cdk5 and p25/Generation of CDK5 and p25
Recombinant Baculovirus

Based on the reported sequences of human CDK5 and p35, GenBank accession numbers X66364 and X80343 respectively, 5 oligonucleotide primers flanking the coding sequence of each gene were used to amplify CDK5 (5'-GCGATGCAGAAATACGAGAACT-3'; 5'-CCCCACTGTCTCACCCCTCTCAA-3') and p35 (5'-CGGTGAGCGGTTTATCCC-TCC-3'; 5'-GCATTGAATCCTTGAGCCATGACG-3') from a human fetal brain cDNA library (Clontech). p25, a C-terminal proteolytic fragment corresponding to amino acids 99-307 of full-length p35 (Lew, et. al), was PCR subcloned from the p35 sequence using oligonucleotide primers (5'-CGGGATCCATGGCCCCAGCCCCCACCGGCCA-3'; 5'-CCAAGCTTCACCGATCCAGGCCTAG-3'). The p25 PCR product (629bp) 10 was cloned into the pFastBacHTb baculovirus expression vector (Gibco BRL) using *BamHI* and *HindIII*. CDK5 was PCR subcloned using oligonucleotide primers (5'-CGGGATCC -GCCACCATGCAGAAATACGAGAAACTGG-3'; 5'-GGACTAGTCTAGGGCGGAC- 15 AGAAGTCG-3'). The CDK5 PCR product (879 bp) was cloned into 20 the pFastBac1 baculovirus expression vector (Gibco BRL) using *BamHI* and *SpeI*. Recombinant baculovirus expressing human Cdk5 and N-terminally six histidine tagged p25 were generated using the Bac-to-Bac system (Gibco BRL).

25 Expression of P25/CDK5 in insect cells

Coinfections of Hi5 cells by recombinant baculovirus containing the P25 gene and another containing the CDK5 gene were done at a multiplicity of infection of 5 (each virus). The Hi5 cultures were set to a cell concentration of 1×10^6 30 cells per ml in 800 ml of Excell media by JRH. The cultures were grown in 2.6L farnbach flasks with shaking (110 rpm) at 27°C for 60 h. The cells were harvested by centrifugation.

Purification of complexes

All steps were performed at 4°C. Insect cells expressing either cyclin E2/CDK2 or p25/CDK5 were lysed using a microfluidizer (Microfluidics Corporation.) The 5 lysis buffer contained 10 mM Hepes, 150 mM NaCl, 20 mM MgCl₂, 20 mM imidazole, 0.5 mM EDTA, 10% glycerol, 25 µg/ml Aprotinin, 25 µg/ml Leupeptin, 1mM Pefabloc, pH 7.5). Total protein was determined on the resulting lysate using the Bradford method with a BSA standard curve. Protamine 10 sulfate was added to the lysate to give a final 30:1 protein:protamine sulfate, incubated for 15-20 min and centrifuged at 14000xg for 30 min to remove insoluble material. Ni-NTA superflow resin (Qiagen Inc) was equilibrated in lysis buffer and incubated with the 15 centrifugation supernatant for 1 h while rotating. The slurry was packed in a glass column and washed until a stable UV baseline was reached. Proteins were eluted with a linear gradient of 20-300 mM imidazole over 15 column volumes. Fractions were analyzed by SDS-PAGE and Western 20 blot. Appropriate fractions were pooled, total protein determined, and submitted for kinase assay.

CDK2 Kinase Assay

CDK2 kinase assays were carried out with inhibitor 25 (dissolved in DMSO) in a total volume of 50 µl with 1 nM enzyme (His-tagged cyclin 2/CDK2), 1 µM Histone-H1 (Gibco), 25 µM ATP, 20 µCi/ml ³³P-ATP (Amersham; 2500 Ci/mmol) in kinase buffer (50 mM Tris-HCl, pH 7.5, 5 mM MgCl₂, 1 mM EGTA, 5 mM DTT, 200 µg/ml BSA and 20 mM β-glycerophosphate 30 for 60 min at 25 °C. Reactions were stopped by the addition of an equal volume of 30% trichloroacetic acid (Sigma). Precipitates were formed by incubation at 4 °C for 60 min then collected by filtration on Millipore® filter plates (MAFC NOB10). MicroScint-20 (40 µL, Packard) was added, and

counted on a Packard TopCount®. Raw cpms were analyzed with a four-parameter logistic fit using the Levenburg Marquardt algorithm (Xlfit software IDBS LTD). Kinetic parameters were calculated by non-linear regression analysis using 5 Grafit (Erihacus Software LTD). Riscovitine (BIOMOL Research Labs Inc., Plymouth Meeting, PA.) and staurosporin (Sigma, St. Louis MO) were used as standards.

CDK5 Kinase Assay

10 CDK5 kinase assays were carried out with inhibitor (dissolved in DMSO) in a total volume of 50 µl with 1 nM enzyme (His-tagged p25/CDK5), 1 µM Histone-H1 (Gibco), 25 µM ATP, 20 µCi/ml ³³P-ATP (Amersham; 2500 Ci/mmol) in kinase buffer (50 mM Tris-HCl, pH 7.5, 5 mM MgCl₂, 1 mM EGTA, 5 mM 15 DTT, 200 µg/ml BSA and 20 mM β-glycerophosphate) for 60 min at 25°C. Reactions were stopped by the addition of an equal volume of 30% trichloroacetic acid (Sigma). Precipitates were formed by incubation at 4 °C for 60 min then collected by filtration on Millipore® filter plates (MAFC NOB10). 20 MicroScint-20 (40 µL, Packard) was added, and counted on a Packard TopCount®. Raw cpms were analyzed with a four-parameter logistic fit using the Levenburg Marquardt algorithm (Xlfit software IDBS LTD). Kinetic parameters were calculated by non-linear regression analysis using 25 Grafit (Erihacus Software LTD). Riscovitine (BIOMOL Research Labs Inc., Plymouth Meeting, PA.) and staurosporin (Sigma) were used as standards.

Examples 235-236, 238, 242, 245, 247-251, 258, 263-268, 270, 273-275, 279, 280-282, 287-288, 291-302, 304, 307-311, 316-317, 319-322, 324-325, 327-330, 332-335, 337-338, 340-343, and 346-347 exhibited cdk2/cyclin kinase activity with IC₅₀ values less than 0.5 µM. The compounds of examples 235-240, 242, 245, 247-251, 258, 263-268, 273-275, 280, 282, 286-288, 291-302, 304, 307-313, 315-317, 319-322, 324-325,

328-330, 332-335, 337-338, 340-343, and 345-347 exhibited cdk5/p25 kinase activity with IC_{50} values less than 0.5 μM .

CELL PROLIFERATION ASSAY

5

Cell proliferation was measured using a colorimetric immunoassay (B/M Roche #164 7229), based on the measurement of pyrimidine analog BrdU incorporation during DNA synthesis in proliferating cells. Cells, e.g., human PC-3 prostate carcinoma cells, huFFS normal human foreskin fibroblast cells, HCT 116 human colon carcinoma cells or HT 29 human colon carcinoma cells, were cultured in a 96-well plate for 24 h, until a cell count of 3×10^3 to 6×10^3 cells per well in duplicate wells were achieved, in a well volume of 200 μl .

10 15 The media was changed and 1 μl of 200X control inhibitors or compounds was added to each well. Cells are incubated for 48 h at 37°C. The cells were labeled with BrdU for 4 h at 37°C. The labeling medium was removed and in one step, the cells were fixed and the DNA was denatured (30 min at RT).

20 25 Anti-BrdU-POD antibody was added to bind to the BrdU incorporated in newly synthesized cellular DNA (60-90 min at RT). The cells were washed 3X with washing buffer, substrate (100 μl) was added and the cells were incubated for 10 min at RT. The substrate reaction was stopped by adding 25 μl of 1M H_2SO_4 . The amount of BrdU incorporated was quantified by measuring the absorbance at 450 nm using ELISA reader.

IC_{50} 's were calculated using GraFit (Sigma).

ISCHEMIC STROKE MODEL: MIDDLE CEREBRAL ARTERY OCCLUSION

30

(MCAO) IN VIVO

The compounds' effect on treating stroke was measured in a MCAO rat model. (L. Belayev et al., Stroke, 27, 1616-23 (1996). Male Sprague-Dawley rats (300-330g body weight) were

anesthetized with halothane and MCAo was induced by inserting a poly-L-lysine coated monofilament suture to the beginning of the middle cerebral artery (MCA). After various time points (60, 90 or 120 min), the intraluminal suture was 5 carefully removed to start reperfusion. Physiological conditions (blood O₂, CO₂, pH, glucose, blood pressure) were monitored and kept stable during the surgery. The compound was dissolved in 20% Captisol in phosphate buffered saline and administered (orally, IV or IP) 90 min after ischemia 10 onset, at the beginning of reperfusion. Further dosing occurred at 4-8 h and twice a day thereafter.

The use of behavioral tests was directly analogous to the clinical neurological examination for assessing ischemic deficits and rates of behavioral recovery. The battery 15 consisted of four tests: (1) postural reflex test, (2) forelimb placing test (JB Bederson et al., *Stroke*, 17:472-76 (1986) (L. Belayev et al., *Stroke*, 26:2313-20 (1995), (3) contralateral foot fault index (A. Tamura et al., *J. Cereb Blood Flow Metab.*, 1:53-60 (1981) (DM Freeney, *Science*, 20 217:855-57 (1982), and (4) cylinder asymmetry (TA Jones and T. Schallert, *J. Neurosci.*, 14:2140-52 (1994). Tests were performed once a day for three days and then once a week for a period of 30 days. These tests are useful in assessing 25 neurological deficits for short-term studies; the cylinder asymmetry test appeared to be the most useful for long term experiments.

At the end of the experiment, the infarct volume was measured (JB Bederson et al., *Stroke*, 17:1304-8 (1986) (KA Osborne et al., *J. Neurol Neurosurg. Psychiatry*, 50:402 30 (1987) (RA Swanson et al., *J. Cereb. Blood Flow Metab.*, 10:290-3 (1990). The brains were removed and sliced coronally at 1 mm thickness. The brain slices were stained with 2% (w/vol) 2,3,5-triphenyltetrazolium chloride (TTC) which stains the infarcted areas of the brain in white and

allows for the measurement of infarct volume by an image-analysis system. Edema volume that contributes to infarct volume was subtracted by comparison with the total volume of the contralateral hemisphere.

5

Formulations

Also embraced within this invention is a class of pharmaceutical compositions comprising the active compounds of Formula I-V in association with one or more non-toxic, 10 pharmaceutically-acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients. The active compounds of the present invention may be administered by any suitable route, preferably in the form 15 of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The compounds and compositions of the present invention may, for example, be administered orally, mucosally, topically, rectally, pulmonarily such as by inhalation spray, or 20 parentally including intravascularly, intravenously, intraperitoneally, subcutaneously, intramuscularly intrasternally and infusion techniques, in dosage unit formulations containing conventional pharmaceutically acceptable carriers, adjuvants, and vehicles.

25 The pharmaceutically active compounds of this invention can be processed in accordance with conventional methods of pharmacy to produce medicinal agents for administration to patients, including humans and other mammals.

30 For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient.

Examples of such dosage units are tablets or capsules. For example, these may contain an amount of active ingredient from about 1 to 2000 mg, preferably from about 1 to 500 mg, more preferably from about 5 to 150 mg. A suitable daily 5 dose for a human or other mammal may vary widely depending on the condition of the patient and other factors, but, once again, can be determined using routine methods.

The amount of compounds which are administered and the dosage regimen for treating a disease condition with the 10 compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the type of disease, the severity of the disease, the route and frequency of administration, and the particular compound employed. Thus, 15 the dosage regimen may vary widely, but can be determined routinely using standard methods. A daily dose of about 0.01 to 500 mg/kg body weight, preferably between about 0.5 and about 50 mg/kg body weight and most preferably between about 0.1 to 20 mg/kg body weight, may be appropriate. The 20 daily dose can be administered in one to four doses per day.

For therapeutic purposes, the active compounds of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of 25 administration. If administered per os, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, 30 gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided

in a dispersion of active compound in hydroxypropylmethyl cellulose.

In the case of psoriasis and other skin conditions, it may be preferable to apply a topical preparation of 5 compounds of this invention to the affected area two to four times a day.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin (e.g., liniments, lotions, 10 ointments, creams, or pastes) and drops suitable for administration to the eye, ear, or nose. A suitable topical dose of active ingredient of a compound of the invention is 0.1 mg to 150 mg administered one to four, preferably one or two times daily. For topical 15 administration, the active ingredient may comprise from 0.001% to 10% w/w, e.g., from 1% to 2% by weight of the formulation, although it may comprise as much as 10% w/w, but preferably not more than 5% w/w, and more preferably from 0.1% to 1% of the formulation.

20 When formulated in an ointment, the active ingredients may be employed with either paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, 25 for example at least 30% w/w of a polyhydric alcohol such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol, polyethylene glycol and mixtures thereof. The topical formulation may desirably include a compound which enhances absorption or penetration of the active ingredient 30 through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogs.

The compounds of this invention can also be administered by a transdermal device. Preferably transdermal

administration will be accomplished using a patch either of the reservoir and porous membrane type or of a solid matrix variety. In either case, the active agent is delivered continuously from the reservoir or microcapsules through a membrane into the active agent permeable adhesive, which is in contact with the skin or mucosa of the recipient. If the active agent is absorbed through the skin, a controlled and predetermined flow of the active agent is administered to the recipient. In the case of microcapsules, the encapsulating agent may also function as the membrane.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier, it may comprise a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make-up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations. Emulsifiers and emulsion stabilizers suitable for use in the formulation of the present invention include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate, sodium lauryl sulfate, glyceryl distearate alone or with a wax, or other materials well known in the art.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus, the cream should preferably be a non-greasy, non-staining and washable product with

suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl 5 myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters may be used. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft 10 paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredients are dissolved or suspended in suitable carrier, 15 especially an aqueous solvent for the active ingredients. The active ingredients are preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% and particularly about 1.5% w/w.

Formulations for parenteral administration may be in 20 the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules using one or more of the carriers or diluents mentioned for use in the formulations for oral administration or by using 25 other suitable dispersing or wetting agents and suspending agents. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, tragacanth gum, and/or various buffers. 30 Other adjuvants and modes of administration are well and widely known in the pharmaceutical art. The active ingredient may also be administered by injection as a composition with suitable carriers including saline, dextrose, or water, or with cyclodextrin (ie. Captisol),

cosolvent solubilization (ie. propylene glycol) or micellar solubilization (ie. tween 80).

The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic 5 parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as 10 a solvent or suspending medium. For this purpose any bland fixed oil may be employed, including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

For pulmonary administration, the pharmaceutical 15 composition may be administered in the form of an aerosol or with an inhaler including dry powder aerosol.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable non-irritating excipient such as cocoa butter and polyethylene 20 glycols that are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

The pharmaceutical compositions may be subjected to conventional pharmaceutical operations such as 25 sterilization and/or may contain conventional adjuvants, such as preservatives, stabilizers, wetting agents, emulsifiers, buffers etc. Tablets and pills can additionally be prepared with enteric coatings. Such compositions may also comprise adjuvants, such as wetting, 30 sweetening, flavoring, and perfuming agents.

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds. Variations and changes which are obvious to one skilled in the art are intended to be within the scope and

nature of the invention which are defined in the appended claims.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this
5 invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

All mentioned references, patents, applications and publications, are hereby incorporated by reference in their
10 entirety, as if here written.